



# **‘TENORMIN’**

atenolol

a comprehensive review



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## Introduction

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It was another twelve years before this theory was confirmed by the work of Black whose special interest

smooth muscle relaxation and decreased blood pressure produced by isoprenaline,<sup>3</sup> might be the key to the development of more therapeutically useful drugs.<sup>2</sup>

The result of further research was the synthesis, in 1960, of pronethalol which inhibited the effects of sympathomimetic amines and sympathetic nervous stimulation on the heart.<sup>4,5</sup> Propranolol followed in 1962 and clinical studies showed it to be effective initially in the treatment of angina. During the late 1960s Lands and co-workers<sup>6</sup> further suggested that beta-receptors could

distinguish more specifically such as the  $\beta_1$ -receptor

Since the introduction of 'Tenormin' into clinical practice in 1976, it has firmly established itself as the world's most widely-prescribed, cardioselective beta-blocker and has clearly demonstrated its efficacy in the

The aim of this book is to comprehensively review the pharmacological properties of 'Tenormin' (the importance of cardioselectivity, hydrophilicity and lack

# References

- 1 AHLQUIST RP  
A study of the adrenotropic receptors  
*Am J Physiol* 1948, **153** 586-600
- 2 SHANKS RG  
The properties of beta-adrenoceptor antagonists  
*Postgrad Med J* 1976, **52** (Suppl 4) 14-20
- 3 POWELL CE and SLATER IH  
Blocking of inhibitory adrenergic receptors by a  
dichloro analog of isoproterenol  
*J Pharmacol Exp Ther* 1958, **122** 480-83
- 4 BLACK JW and STEPHENSON JS  
Pharmacology of a new adrenergic beta-receptor  
blocking compound (Nethalide)  
*Lancet* 1962, **2** 311-14
- 5 ALLEYNE GAO, DICKINSON CJ  
DORNHURST AC *et al*  
Effect of pronethalol in angina pectoris  
*Br Med J* 1963, **2** 1226
- 6 LANDS AM, LUDUENA PP and BUZZO HJ  
Differentiation of receptors responsive to  
isoproterenol  
*Life Sci* 1967, **6** 2241-49

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**'Tenormin'**  
**The advantages**  
**of cardioselectivity**

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## Clinical relevance of cardioselectivity

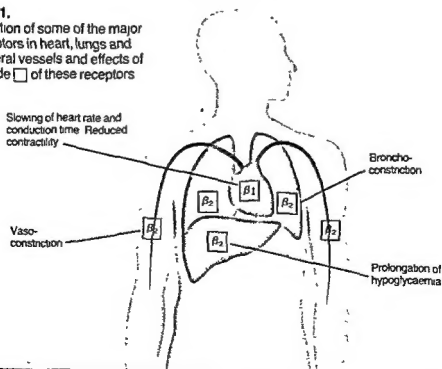
Ever since Lands in 1967 proposed the existence of two types of beta-receptor with  $\beta_1$ -receptors occurring predominantly in the heart and  $\beta_2$ -receptors predominantly in the periphery, it has been theoretically desirable for a beta-blocker to possess the property of *cardioselectivity*. This is defined as the ability to block preferentially the cardiac  $\beta_1$ -receptors at doses which leave the peripheral  $\beta_2$ -receptors relatively unaffected. The distribution of some of the main  $\beta_1$ - and  $\beta_2$ -receptors is shown below (Figure 1).

A beta-blocking agent which is non-selective might be expected to confer all the benefits of  $\beta_1$ -blockade but

hypoglycaemia.<sup>3</sup>

Although the property of cardioselectivity is relative rather than absolute, 'Tenormin' is one of the most cardioselective beta-blockers yet to become available for clinical use

**Figure 1.**  
Distribution of some of the major  $\beta$ -receptors in heart, lungs and peripheral vessels and effects of blockade of these receptors



This has been demonstrated in a quantitative model in

obstruction and will be described below. They have also been reviewed by Cruickshank<sup>1</sup>

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## Cardioselective 'Tenormin' has little effect on lung function

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### Volunteer studies

The bronchus represents a clinically relevant

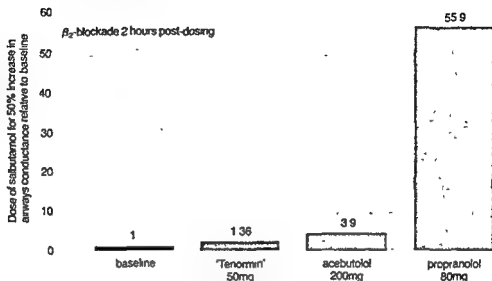
measuring the dose of an inhaled beta-stimulant required to produce 50% of maximal bronchodilator response during treatment with one of several beta-blockers

Studies from this group<sup>2</sup> have shown that the dose of salbutamol required for a 50% increase in airways conductance, relative to baseline, was 41 times greater after 80mg propranolol than after 50mg 'Tenormin' (Figure 2) These two doses produced equivalent beta<sub>1</sub>-blockade

Using the same model, Harrison and Tattersfield<sup>4</sup> have compared 'Tenormin' with another selective agent, metoprolol. Salbutamol dose response curves were

exerted the same degree of beta<sub>1</sub>-blockade. However,

**Figure 2.**  
Comparison of propranolol, acebutolol and 'Tenormin'  
on airways function in volunteers<sup>2</sup>



*"On available evidence atenolol ['Tenormin'] and*

*The relevance of these studies depends on the*

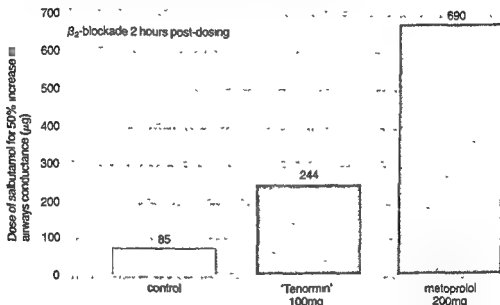
*Although this assumption is difficult to prove, the investigators point out that, "... clinical studies of oral beta-adrenoceptor antagonists in patients with asthma are in good general agreement with our findings."*<sup>6</sup>

## Acute studies in asthmatics

*The implications of cardioselectivity for the asthmatic have been illustrated by Benson *et al*.<sup>7</sup> They showed that*

These patients (termed "*responders*") reacted badly to non-selective beta-blockers whether or not intrinsic sympathomimetic activity (ISA) was present (eg pindolol). In a randomised, crossover comparison of propranolol, pindolol, acebutolol and 'Tenormin' in 12 patients with asthma,<sup>7</sup> bronchoconstriction in the five "*responding*" patients was greatest following propranolol and least following 'Tenormin', the only drug which did not differ significantly from placebo.

**Figure 3.**  
Comparison of 'Tenormin' (100mg) and metoprolol (200mg) on airways function in volunteers 2 hours after dosing<sup>4</sup>



Even more important is the fact that only the non-selective drugs, 'Tenormin' and acebutolol

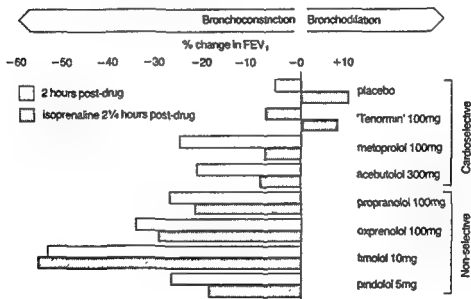
These results were confirmed in a similar study<sup>10</sup> in ten asthmatic patients, comparing 'Tenormin', metoprolol,

significantly from placebo (Figure 4). Furthermore,

'Tenormin' was the only drug not to cause wheezing and  
 not to differ from placebo in response to inhaled

studies in patients with airways obstruction by several  
 other workers 11-20

**Figure 4.**  
 Effects of  $\beta$ -blocker and isoprenaline on FEV<sub>1</sub> in 10  
 "responding" (labile) asthmatic patients<sup>10</sup>

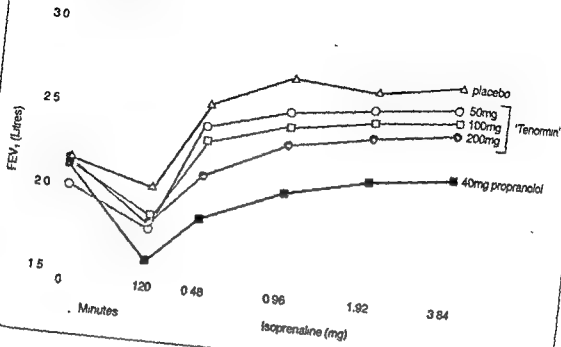


100 90 80 70 60 50 40 30 20 10 0

controlled study in ten patients with hypertension and



**Figure 5.**  
Inhaled isoprenaline dose-response curves in ten  
asthmatic hypertensives<sup>21</sup>



### Chronic studies in asthmatics

Lawrence *et al*<sup>22</sup> compared  
doses of 100mg

...ing per  
...  
... who  
... with a beta<sub>2</sub>  
...  
...

**Table 1. Comparison of 'Tenormin' and metoprolol, given chronically, on respiratory function in asthmatic hypertensives<sup>22</sup>**

	Total no. of asthmatic attacks (n=13)	Total no of asthma-free days (n=13) metoprolol	% time with v. severe, severe or moderate wheeze (n=12)
'Tenormin'	244	219	50
metoprolol	298	199	74
placebo	272	217	60
Statistically significant	MvP NS MvT p<0.05 TvP NS	NS p<0.05 NS	NS p<0.05 NS

T = 'Tenormin' M = metoprolol P = placebo NS = non-significant

## Conclusion

*since cardioselectivity is dose-related and a  $\beta_{2}$ -stimulant should be available for use if indicated*

## **Cardioselective 'Tenormin' and delay of recovery from hypoglycaemia**

Diabetic patients show a high prevalence of

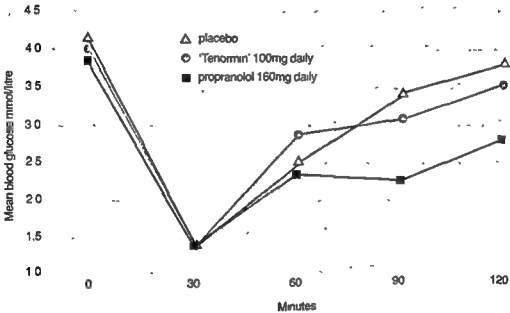
reflex bradycardia during hypoglycaemia. The property of cardioselectivity has a marked influence on these potential complications



# Duration of hypoglycaemia

agents.

**Figure 6.**  
Effect of 'Tenormin' and propranolol on insulin-induced hypoglycaemia in normal subjects<sup>26</sup>



## Signs and symptoms of hypoglycaemia

Acute hypoglycaemia results in the release of several hormones including catecholamines in an effort to raise blood glucose levels. The catecholamine induced surge of

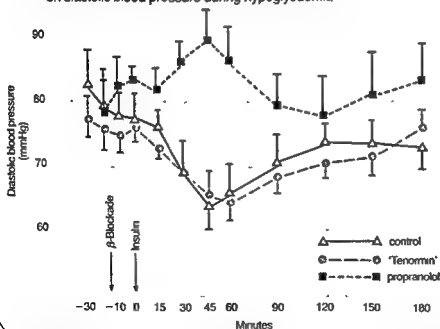
... which may

... decreased

is preserved and this constitutes an important advantage of a selective agent such as 'Tenormin' in diabetics.

... by *Quinlan et al*<sup>27</sup>

**Figure 7.**  
Comparison of effects of 'Tenormin' and propranolol on diastolic blood pressure during hypoglycaemia<sup>27</sup>



## Conclusion

*When compared with non-selective beta-blockers, it would appear that a cardioselective beta-blocker such as 'Tenormin' is less likely to delay the recovery from hypoglycaemia and may also be less likely to block the warning signs, eg tremor. The lack of diastolic pressor*

## Cardioselective 'Tenormin' in beta<sub>2</sub>-vasodilatory-mediated stress situations

Stress situations which increase adrenaline secretion,

### Cigarette smoking

The cardiovascular responses to smoking during acute

study.<sup>35</sup> Propranolol, but not 'Tenormin', caused a

*the management of patients who are habitual smokers*,<sup>35</sup> (see Footnote, page 16).

In an evaluation of chronic oral drug administration (at least four weeks' treatment with propranolol 160mg

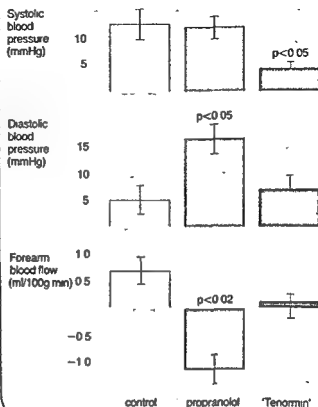
( $p < 0.0003$ ) with 'Tenormin' lower than the non-selective

about 15 minutes) and so the initial effect became diluted when the longer time period was considered

### Smoking and coffee drinking

(Figure 9).

**Figure 8.**  
Haemodynamic changes in 7 habitual smokers  
following intravenous doses of 'Tenormin' and  
propranolol<sup>35</sup>



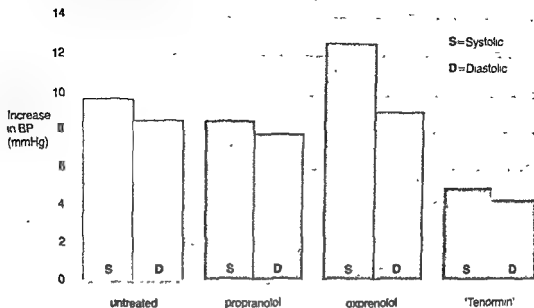
and reversing the peripheral vasoconstrictor effects of nicotine.

Furthermore, *Beta*<sub>1</sub>-selective blockade with atenolol

Other recent studies<sup>38,39</sup> have also confirmed the therapeutic advantage of cardioselective drugs such as 'Tenormin' in hypertensives who smoke

**Figure 9.**

Mean change in blood pressure from placebo values (orange juice) in 8 hypertensive habitual smokers 5-120 minutes after coffee plus smoking<sup>37</sup>



## Conclusion

Low-dose cardioselective 'Tenormin' and exercise capacity

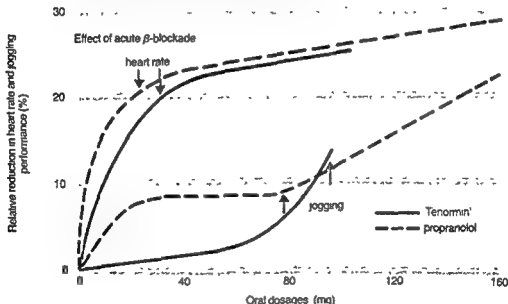
### Low-dose cardioselective 'Tenormin' and exercise capacity

'Tenormin' causes less fatigue than non-selective beta-blockers in hypertensive patients

Work from Sweden<sup>40</sup> has shown that long-distance runners have a predominance of slow twitch muscle fibres whereas sprinters have a predominance of fast twitch fibres. In the slow twitch fibre, metabolic

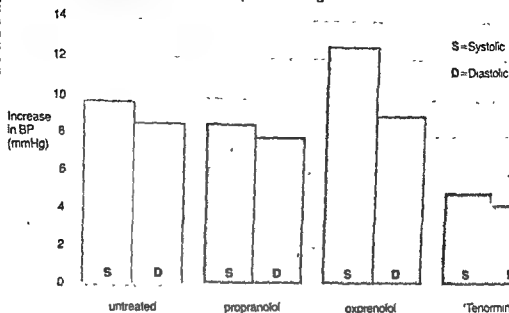
A beta<sub>2</sub>-component seems likely in this process and indeed the performance of long distance runners is

**Figure 10.**  
The effects of short-term non-selective and  $\beta_1$ -selective blockade on jogging in healthy young men<sup>40</sup>



Other investigators have confirmed that

**Figure 9.**  
Mean change in blood pressure from placebo values  
(orange juice) in 8 hypertensive habitual smokers  
5-120 minutes after coffee plus smoking<sup>37</sup>



## Conclusion

For dose-response studies, the results of the present study suggest that the difference between propranolol and 'Tenormin' is not statistically significant. However, the results of the present study suggest that the difference between propranolol and 'Tenormin' is not statistically significant. However, the results of the present study suggest that the difference between propranolol and 'Tenormin' is not statistically significant.

## Low-dose cardioselective 'Tenormin' and exercise capacity

The results of the present study suggest that the difference between propranolol and 'Tenormin' is not statistically significant. However, the results of the present study suggest that the difference between propranolol and 'Tenormin' is not statistically significant.

\*Longer-term studies carried out by the same workers (ref.35a) suggest that the difference between propranolol and 'Tenormin', seen acutely, may diminish with chronic beta-blockade treatment.

## Lipoproteins

Beta-blocker therapy has been associated with an

factor, low-density-lipoprotein (LDL) cholesterol was not consistently affected by beta-blockade and was

relevance of these changes is uncertain, particularly in view of the evidence for a cardioprotective effect of beta-blockade (See 'Myocardial Infarction' chapter)

### Summary: 'Tenormin' – the advantages of cardioselectivity

- allows a wide patient selection
- ability to be prescribed, with care, to patients with potential airways problems
- can be prescribed in insulin-dependent diabetics
- may be preferable in hypertensives who smoke and drink coffee
- minimal reduction in physical performance with low dose 'Tenormin'



tolerance. The fatiguing effect of non-selective blockade persisted during training and limited the effect of the training programme to a greater extent than 'Tenormin'.

## Conclusion

*Muscle fatigability was less with 'Tenormin' than with*

*in physically active hypertensives since, compared with non-selective agents, it interferes less with the various metabolic processes supplying the muscles with energy*

## The effect of cardioselective

### 'Tenormin' on other variables

## Cold extremities and Raynaud's phenomenon

All beta-blockers cause cold extremities in some patients Marshall *et al*<sup>12</sup> have indicated that this may be less of a

## Renal function

Although there is some controversy over the effects of beta-blockers on renal function and renal blood flow, the consensus of opinion seems to be that, at least in the

clearance  $\rightarrow$

With 'Tenormin' there was no significant

this dose. With 'Tenormin' there was no significant

increased by an average of 9% but remained within the

cardioselective agent.

- therapy  
*Postgrad Med J* 1977, **53** (Suppl 3) 102-10
- 25 RUFFIN RE, MCINTYRE ELM, LATIMER KM, WARD HE, CROCKETT AJ and ALPERS JH  
Assessment of  $\beta$ -adrenoceptor antagonists in asthmatic patients  
*Br J Clin Pharmacol* 1982, **13** 325s-35s
  - 26 DEACON SP and BARNETT D  
Comparison of atenolol and propranolol during insulin-induced hypoglycaemia  
*Br Med J* 1976, **2** 272-73
  - 27 LAURIDSEN UB, CHRISTENSEN NJ and LYNDSOE J  
Effects of non-selective and  $\beta_1$ -selective blockade on glucose metabolism and hormonal response during insulin-induced hypoglycaemia in normal man  
*J Clin Endocrinol Metab* 1983, **56** 876-82
  - 28 DEACON SP, KARUNANAYAKE A and BARNETT D  
Acebutolol, atenolol and propranolol and metabolic responses to acute hypoglycaemia in diabetics  
*Br Med J* 1977, **2** 1255-57
  - 29 DEACON SP  
Effect of atenolol and other beta blockers on insulin-induced hypoglycaemia  
*Proc R Soc Med* 1977, **70** (Suppl 5) 50-52
  - 30 STROM L  
Propranolol in insulin-dependent diabetes  
*N Engl J Med* 1978, **299** 487
  - 31 KOLENDORF J, AERENLUND JENSEN H, HOLST JJ and POULSEN JE  
Effect of acute selective beta-adrenoceptor blockade on hormonal and cardiovascular response to insulin-induced hypoglycaemia in insulin-dependent diabetic patients.  
*Scand J Clin Lab Invest* 1982, **42** 69-74
  - 32 PAPE J  
Blood pressure and pulse response to insulin-induced hypoglycaemia during non-selective and selective beta-blockade  
*Acta Med Scand* 1981, **645** (Suppl 1) 105-108
  - 33 NILSSON OR, KARLBERG BE and SODERBERG A  
Plasma catecholamines and cardiovascular responses to hypoglycaemia in hyperthyroidism before and during treatment with metoprolol and propranolol  
*J Clin Endocrinol Metab* 1980, **50** 906-91
  - 34 RYAN JR, LACORTE W, JAIN A and MCMAHON FG  
Response of diabetics treated with atenolol or propranolol to insulin-induced hypoglycaemia.  
*Drugs* 1983, **25** (Suppl 2) 256-57
  - 35 FREESTONE S and RAMSAY LE  
Effect of chronic  $\beta$ -blockade on the pressor response to cigarette smoking  
*Br J Clin Pharmacol* 1983, **15** 596p-97p
  - 36 CUSPIDI S, ALIPRANDI FL, CAVALLINI F and SAMPIERI L  
Effects of short- and long-term  $\beta$ -blockade on changes in blood pressure caused by cigarette smoking in normotensive and hypertensive subjects  
*Drugs* 1983, **25** (Suppl 2) 148-49
  - 37 FOGARI I, PARINI A and FINARDI G  
Cardiovascular response to cigarette smoking during adrenergic block in essential hypertension.  
*Drugs* 1983, **25** (Suppl 2) 149-50
  - 38 KARLSSON J  
Effects of  $\beta$ -adrenoceptor blockade on exercise performance and metabolism.  
*Clin Sci* 1981, **61** 299

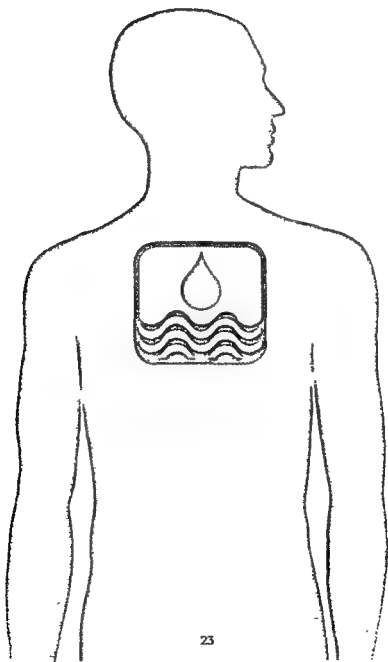
# References

1. CRUICKSHANK JM  
The clinical importance of cardioselectivity and lipophilicity in beta-blockers  
*Am Heart J* 1980, 100 160-78
2. TATTERSFIELD AE, MACKAY AD, GRIBBIN HR and BALDWIN CJ  
The cardioselectivity of atenolol and metoprolol  
*Br J Clin Pharmacol* 1981, 12 61-65
3. TATTERSFIELD AE and HARRISON RN  
Effect of  $\beta$ -blocker therapy on airway function  
*Drugs* 1983, 25 (Suppl 2) 227-31
4. HARRISON RN and TATTERSFIELD AE  
The cardioselectivity of atenolol and metoprolol at 2 and 24 hours after a single dose  
*Br J Clin Pharmacol* 1981, 12 61-65
5. TATTERSFIELD AE  
Beta-blockers and chest disease: the patient at risk  
*Mod Med* 1983, 28 10
6. GRIBBIN HR, MACKAY AD, BALDWIN CJ and TATTERSFIELD AE  
Bronchial and cardiac  $\beta$ -adrenoceptor blockade—a comparison of atenolol, acebutolol and labetalol  
*Br J Clin Pharmacol* 1981, 12 61-65
7. BENSON MK, BERRILL WT, CRUICKSHANK JM and STERLING GS  
A comparison of four  $\beta$ -adrenoceptor antagonists in patients with asthma  
*Br J Clin Pharmacol* 1978, 5 415-19
8. BENSON MK  
Cardioselectivity studies.  
*Proc R Soc Med* 1977, 70 48
9. ORMEROD LP and STABLEFORTH DE  
Asthma mortality in Birmingham 1975/7: 53 deaths  
*Br Med J* 1980, 280 687-96
10. BENSON MK  
Beta-blockers and asthma  
*Br Heart J* 1978, 40 184-89
11. ASTROM H  
Comparison of the effect on airway conductance of a new selective beta-adrenergic blocking drug, atenolol, and propranolol in asthmatic subjects  
*Scand J Respir Dis* 1975, 56 292-96
12. HUGHES FC, JULIEN P, BORS V and MARCHE J  
Effets des differents beta-bloqueurs sur le debit expiratoire de l'asthmatique  
*Therapie* 1976, 31 595-603
13. VILSVIK JS and SCHAANNING J  
The effect of atenolol on ventilatory and cardiac function in asthma  
*Br Med J* 1976, 2 453-55
14. SVEDMYR N  
Comparacao entre o efeito do atenolol e do metoprolol na funcao pulmonar em p  
*Rev Bras Med* 1980, 37 305-306
15. GREEFHORST PPM and VAN HERVAARDEN CLA  
Comparative study of the ventilatory effects of three beta-selective blocking agents in asthmatic patients  
*Eur J Clin Pharmacol* 1981, 20 417-21
16. SUZUKI S, MEUT, CHMI K et al  
Effect of atenolol on pulmonary function in asthma  
*Acta Ther* 1981, 7 55-65
17. LOFDAHL CG and SVEDMYR N  
Cardioselectivity of atenolol and metoprolol: A study in asthmatic patients  
*Eur J Respir Dis* 1981, 92 396-404
18. PERKS WH, CHATTERJEE SS, CROXSON RS and CRUICKSHANK JM  
A comparison of atenolol and propranolol in patients with asthma  
*Br J Clin Pharmacol* 1978, 5 415-19

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**'Tenormin'**  
**The benefits**  
**of hydrophilicity**

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Br Med J 1976, 1 1498

43 O'MALLEY K, O'CAHILL ACHAM...

44 BELLINI, G, BATTILANA G, CARRETTA R  
*et al*  
Antihypertensive effects and kidney function in  
hypertensive patients treated with atenolol and  
oxprenolol  
*Drugs* 1983, 25 (Suppl 2) 253-55

45 WAAL-MANNING HJ  
Atenolol and three non-selective beta-blockers in  
hypertension  
*Clin Pharmacol Ther* 1979, 25 8-18

46 MUELLER J, BYRNE MJ, VAN SCHALKWYK J  
and OPIE LH  
*Renal* -

47. DE LEEUW PW VAN SOEST...

48 DAY JL, METCALFE J and SIMPSON CN  
Adrenergic mechanisms in control of plasma lipid  
concentrations  
*Br Med J* 1982, 284 1148

*Lancet* 1980, 2 46

50 LOUTCH...

s262-s64 *Drugs* 1982, 4 (Suppl 2)

51 DAY JL, SIMPSON CN, METCALFE J and  
PAGE RL  
Metabolic consequences of atenolol and  
propranolol in treatment of essential  
hypertension  
*Br Med J* 1979, 1 77

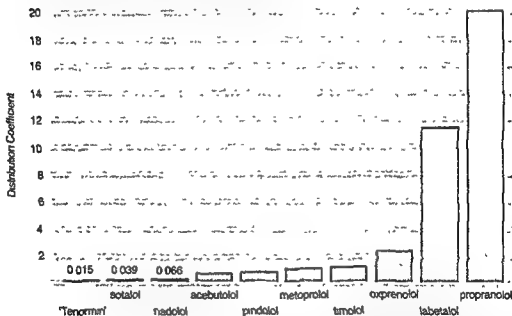
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## Pharmacokinetics

The hydrophilicity of a beta-blocker relates to its distribution or partition in an octanol/aqueous medium. The partition coefficient of a drug is the ratio of its concentration in octanol and water and the lower the value, the more water soluble is the drug. The "distribution coefficient" of a compound is more relevant to biological systems since it also takes into account pH and temperature.

Woods and Robinson have calculated the distribution coefficients for most commonly available beta-blockers, the most hydrophilic being 'Tenormin' (Figure 1)<sup>1</sup>

**Figure 1.**  
Distribution coefficients in octanol/aqueous buffer  
(pH 7.4 and 37°C) for several beta-blockers



**Hydrophilicity gives more consistent pharmacokinetics than lipophilic agents**

The extent of myocardial lipid accumulation is directly related to the lipophilicity of the drug.

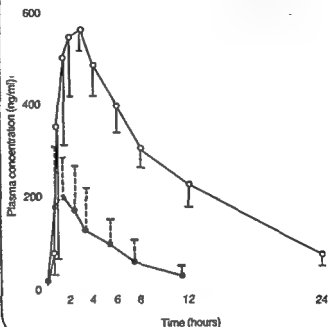
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**Figure 2.**

Plasma metoprolol concentrations over time in extensive (●) and poor (○) hydroxylators of debrisoquine



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**Long duration of action and  
once-daily dosing give good  
antihypertensive control and  
compliance**

---

However, lipophilic beta-blockers have short plasma half-lives<sup>19</sup> unless used in long-acting formulations.

The longer more predictable pharmacodynamic action of 'Tenormin' can be seen in clinical practice where it produces smooth 24-hour control of blood pressure. For

agents metoprolol and pindolol<sup>20</sup> (Figure 3)



kidneys. 'Tenormin' is only found at extremely low levels in the deeper body compartments, such as the brain<sup>2</sup>

The fact that 'Tenormin' is not found in the brain

## Including predictable blood levels

• The fact that 'Tenormin' is not found in the brain

• The fact that 'Tenormin' is not found in the brain

• The fact that 'Tenormin' is not found in the brain

variability in peak 'Tenormin' blood levels is only about

contrast to 'Tenormin' which undergoes only minimal metabolism

## Even with impaired liver function

In patients with varying degrees of liver function it has been demonstrated that there was a greater variation in peak plasma levels of metoprolol and propranolol than 'Tenormin' and that the kinetics of 'Tenormin' were independent of the liver<sup>7,8</sup>

The small variability in plasma levels of 'Tenormin' helps to explain its narrow dose range compared with the lipophilic beta-blockers which may require titration to suit individual patient needs

## Or with inherent genetic defects in metabolism

Some populations exhibit genetic polymorphism with about 90% being extensive metabolisers of debrisoquine (a genetic defect in drug oxidation)<sup>9</sup>

• The fact that 'Tenormin' is not found in the brain

• The fact that 'Tenormin' is not found in the brain

• The fact that 'Tenormin' is not found in the brain

Further evidence for the superiority of 'Tenormin' over 100 mg metoprolol or 200 mg sustained-release metoprolol was provided by Scott *et al* who showed significantly better blood pressure control over 24 hours with 100 mg 'Tenormin' than either conventional metoprolol or a long-acting formulation <sup>21</sup>

In contrast to the accepted control of hypertension and

prescribed twice-daily in conventional formulations. <sup>23,24</sup>

The predictable clinical response to once-daily 'Tenormin' means that compliance is extremely high. A mean of 92% compliance was reported with 'Tenormin' in one study and this was greater than with conventional propranolol, pindolol, metoprolol or labetalol taken two or three times daily <sup>25</sup>. A high compliance rate (76-88%) was also shown by Ingram in a general practice study involving over 3,000 hypertensive patients <sup>26</sup>

'Tenormin' offers the advantages of a once-daily dosage with consequent convenience for patients.

## Low distribution coefficient leads to low incidence of CNS-related problems

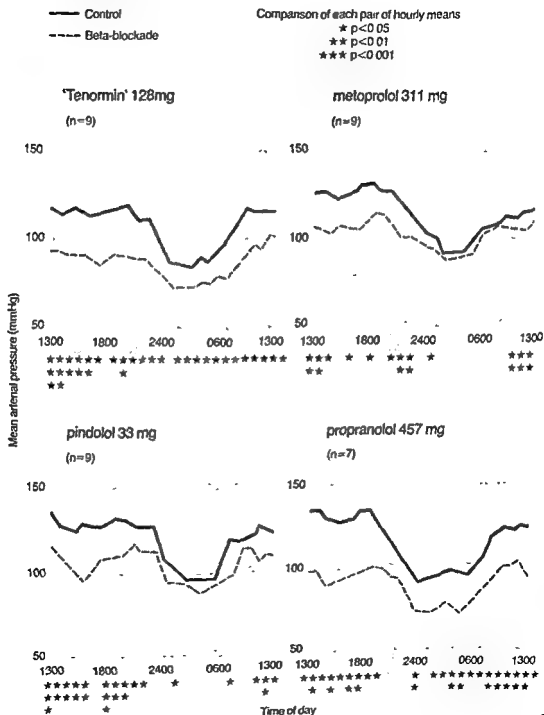
The volume of distribution of beta-blockers in the human body compartment depends on the lipid sol-

**Table 1. Protein binding, lipophilicity and volume of distribution of three beta-blockers.** <sup>5,27-29</sup>

Beta-blocker	Plasma protein binding (%)	Hydrophilic/lipophilic	Volume of distribution (L/kg)
'Tenormin'	3	Very hydrophilic	0.7
metoprolol	10	Lipophilic	5.0
propranolol	90	Very lipophilic	3.6

## High compliance with once-daily 'Tenormin'

**Figure 3.**  
Antihypertensive control during 24 hours.  
Between-patient comparison of four beta-blockers



## Low risk of drug interactions

## 'Tenormin' and psychomotor performance

The water/lipid solubility of a beta-blocker is of

of trials appear in the 'Drug Interactions' chapter

Widely prescribed drugs such as beta-blockers should not adversely influence patients' abilities to perform everyday tasks involving mental skill or manual dexterity. Many validated tests have been devised in order objectively to measure the effects of drugs on human 'psychomotor performance' (CNS arousal and integration). These tests include critical flicker fusion frequency, simple or complex reaction time, visual

level of alertness or arousal which in turn may be affected by drugs acting on the CNS.

*had no adverse effect on reaction times and concentration*<sup>33</sup>

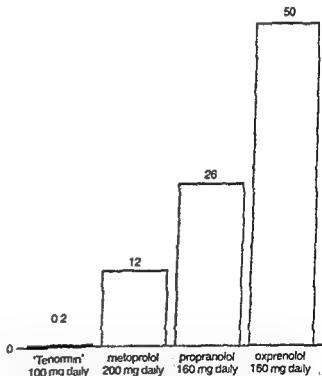
measured using electroencephalograms (EEG), reaction times and critical flicker fusion frequency. Vigilance was found to be impaired in hypertensives compared with normotensive controls. 'Tenormin' induced changes in the EEG, which were interpreted as

The hydrophilic nature of 'Tenormin' means that it only reaches the deeper compartments of the body such as the brain with relative difficulty, as shown by the very low concentrations of the drug in the CNS of rats,<sup>30</sup> cats<sup>31</sup> and man.<sup>2</sup>

into the cerebrospinal fluid and brain tissue was

**Figure 4.**

**Brain/plasma ratios of four beta-blockers**



**Low incidence of CNS side-effects**

## Low risk of drug interactions

## 'Tenormin' and psychomotor performance

The water/lipid solubility of a beta-blocker is of

Widely prescribed drugs such as beta-blockers should not adversely influence patients' abilities to perform everyday tasks involving mental skill or manual dexterity. Many validated tests have been devised in order objectively to measure the effects of drugs on human 'psychomotor performance' (CNS arousal and integration). These tests include critical flicker fusion frequency, simple or complex reaction time, visual reaction time, short- or long-term memory, car driving, pursuit rotor and digit-symbol substitution tests. The performance of these tasks depends on the individual's level of alertness or arousal which in turn may be affected by drugs acting on the CNS.

Many of these tests have also been used to assess the

normotensive and hypertensive patients.

min',

The hypertensive patients

measured using electroencephalograms (EEG), reaction times and critical flicker fusion frequency. Vigilance was found to be impaired in hypertensives compared with normotensive controls. 'Tenormin' induced changes in the EEG.

**Table 2. Effect of 'Tenormin' on various tests of psychomotor function.**

Test procedure	Outcome*	References
Reaction time (simple or complex)	-+	33,35,38
Visual reaction time	+	33
Colour/word test	-	40
Critical flicker fusion	-	34,35,38
EEG changes (vigilance)	+	34
Kinetic visual acuity	-+	37,39
Memory (questionnaire)	+	36
Memory (short/long-term)	-	36,38
Digit-symbol substitution test	-	38
Subjective symptoms of:		
arousal	-	39
relaxation	+	32,39
mood	-+	32,39
sedation/drowsiness	-	32,35
sociability	+	38

\* - = no change    + = improvement

In trials where the psychomotor effects of 'Tenormin' have been compared with other antihypertensive agents, decrements in psychomotor function were observed with methyldopa.<sup>35</sup> The effects of 'Tenormin' and methyldopa were compared with placebo in two identical studies using simple tests of CNS function.<sup>35</sup> One of the conclusions of the trial was that,

"...the effects of 'Tenormin' and methyldopa were compared with placebo in two identical studies using simple tests of CNS function."

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Other work has also indicated a detrimental effect of methyldopa<sup>36,37</sup> as well as propranolol<sup>38</sup> on psychomotor tests

## Effect of 'Tenormin' on driving skills

Driving is one of the most complex psychomotor skills carried out by the average person and requires a good combination of attention, perception and decision

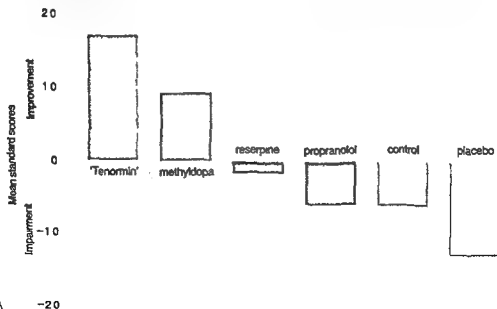
Actual car driving skill was assessed in a double-blind study before and after administration of 'Tenormin'.

questions played simultaneously on a tape recorder),

'Tenormin' significantly improved KVA performance

further volunteer study<sup>39</sup> (see Table 2) 'Tenormin' therefore appears to have no adverse effect or may even improve the ability to recognise the hazard from a moving vehicle.

Figure 5.  
Kinetic visual acuity – mean standard scores





road driving.<sup>37</sup>

Using another test of driving performance, a 10 mg

relevance to actual car driving is highlighted by the

A driving simulator was used to test the performance of normal volunteers while under mental stress. 'Tenormin' did not impair the subjects performance on this test.<sup>38</sup>

## Summary:

### 'Tenormin' – the benefits of hydrophilicity

- Narrow dose range ensures simple prescribing
- Long duration of action means once-daily dosing and therefore high compliance
- Low penetration into brain results in a very low incidence of CNS side-effects
- Psychomotor performance unaffected or even improved as a result of reduced anxiety

# References

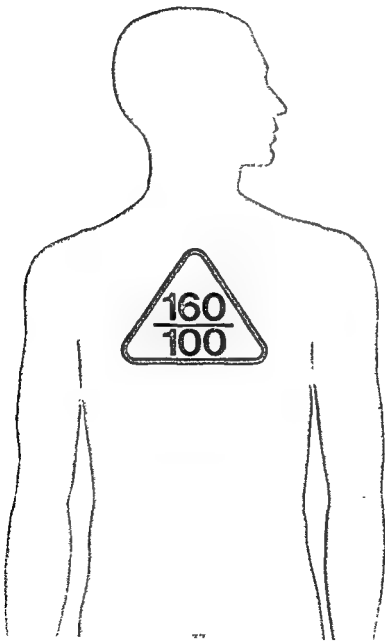
- 2 NEIL-DWYER G, BARTLETT J, McAINSH J and CRUICKSHANK JM  
Beta-adrenoceptor blockers and the blood brain barrier  
*Br J Clin Pharmacol* 1981; 11 549-53
- 3 McAINSH J  
Clinical pharmacokinetics of atenolol  
*Postgrad Med J* 1977; 53 (Suppl. 3) 74-78
- 4 SHAND DG  
Pharmacokinetic properties of the beta-adrenergic receptor blocking drugs  
*Drugs* 1974; 7 39-47
- 5 BROWN HC, CARRUTHERS SG, JOHNSTON GO *et al*  
Clinical pharmacological observations on atenolol, a beta-adrenoceptor blocker  
*Clin Pharmacol Ther* 1976; 20 524-34
- 6 JOHNSON G and REGÄRDH CG  
Clinical pharmacokinetics of beta-adrenoceptor blocking drugs  
*Clin Pharmacokinet* 1976; 1 233-63
- 7 SOTANIEMI EA  
Role of liver enzyme activity in the metabolism of some beta-blocking compounds.  
*Curr Ther Res* 1980; 28 45s-50s
- 8 SOTANIEMI EA, ANTILA M, PELKONEN RO, SAKO II and SUNDOQUIST H  
Role of liver drug metabolism in selection of beta blocking drugs.  
*Clin Pharmacol Ther* 1980; 27 Abstract A 18, 287
- 9 LENNARD MS, SILAS JH, FREESTONE S and TREVETHICK J  
Defective metabolism of metoprolol in poor hydroxylators of debrisoquine  
*Br J Clin Pharmacol* 1982; 14 301-303
- 10 SILAS JH, LENNARD MS, TUCKER GT *et al*  
Why hypertensive patients vary in their response to oral debrisoquine.  
*Br Med J* 1977; 1 422-25
- 12 FREESTONE S, LENNARD MS, SILAS JH and RAMSAY LE  
Duration of beta blockade with metoprolol and atenolol, influence of drug oxidation.  
*Postgrad Med J* 1983; 59 (Suppl. 3) 36-37
- 13 SHANKS R, CARRUTHERS SG, KELLY JG and McDEVITT DG  
Correlation of reduction of heart rate with blood levels of atenolol after oral and intravenous administrations.  
*Postgrad Med J* 1977; 53 (Suppl. 3) 70-73.
- 14 McDEVITT DG, JOHNSTON GD, KELLY JG and SHANKS RG  
Investigation of chronic dosing regimens of atenolol  
*Postgrad Med J* 1977; 53 (Suppl. 3) 79-82.
- metoprolol  
*Clin Pharmacol Ther* 1981; 29 295-302.
- 16 HARRY JD, CRUICKSHANK JM and YOUNG JM  
The relative activities of atenolol and metoprolol on the cardiovascular system of man.  
*Br J Clin Pharmacol* 1980; 9 (3) 296p
- 17 HARRY JD and SHIELDS NG  
Relative activity of atenolol and metoprolol  
*Br Med J* 1978; 2 (6130) 128
- 18 JOHANSSON JR, McCALL M, WILHELMSSON C and VEDIN JA  
Duration of action of beta-blockers  
*Clin Pharmacol Ther* 1980; 27 (5) 593-601
- 19 EVANS GH and SHAND DG  
The disposition of propranolol. Independent variation in steady-state circulating drug concentrations and half-life as a result of plasma binding in man.  
*Clin Pharmacol Ther* 1973; 14 494-500
- 20 FLORAS JS, JONES JV, HASSAN MO and SLEIGHT P  
Ambulatory blood pressure during once-daily randomised double-blind administration of atenolol, metoprolol, pindolol and slow-release propranolol.  
*Br Med J* 1982; 285 1387-92
- 21 SCOTT AK, RIGBY JW, WEBSTER J, HAWKSWORTH GM, PETRIE JC and LOVELL HG  
Atenolol and metoprolol once-daily in hypertension  
*Br Med J* 1982; 284 1514-16
- 22 BARBER JH  
Relative activity of atenolol and metoprolol.  
*Br Med J* 1978; 2 357
- 23 WILCOX RG  
Randomised study of six beta-blockers and a thiazide diuretic in essential hypertension.  
*Br Med J* 1978; 2 383-85

- 24 WILCOX RG and HAMPTON JR.  
Comparative study of atenolol, metoprolol,  
metoprolol durules and slow-release oxprenolol in  
essential hypertension  
*Br Heart J* 1981; 46 498-502.
- 26 INGRAM DF.  
Interim report on a compliance study and a review  
of side-effects  
*Proc R Soc Med* 1977, 70 (Suppl 5) 54-55
- 27 BARBER HE, HAWKSWORTH GM,  
  
*Br J Clin Pharmacol* 1978, 6 446p
- 28 JOHANSSON KA, APPELGREN C, BORG KO  
and ELOFSSON R.  
Binding to two adrenergic beta-receptor antagonists,  
alprenolol and H93/26 to human serum proteins.  
*Acta Pharm Suec* 1974, 11 333-46
- 29 REGÅRDH CG  
Pharmacokinetic aspects of some  $\beta$ -adrenoceptor  
blocking drugs  
*Acta Med Scand* 1982, (Suppl 665) 49-60
- 30 DAY MD, HEMSWORTH BA and STREET JA.  
The central uptake of beta-adrenoceptor antagonists  
(propranolol, practolol, atenolol, oxprenolol,  
acebutolol, metoprolol)  
*J Pharm Pharmacol* 1977, 29 (Suppl) 52p
- 31 VAN ZWETEN PA and TIMMERMANS PB  
Comparison between the acute hemodynamic  
effects and brain penetration of atenolol and  
metoprolol  
*J Cardiovasc Pharmacol* 1979, 1 85-96
- 32 BETTS TA and BLAKE A.  
The psychotropic effects of atenolol in normal  
subjects Preliminary findings  
*Postgrad Med J* 1977, 53 (Suppl 3) 151-56
- 33 HARMS D and FACHALE E.  
The effect of atenolol on reaction times and  
concentration  
*Drugs* 1983, 25 (Suppl 2) 265-67.
- 34 SCHENK GK and ANLAUF M  
Atenolol therapy in hypertensive patients Effects on  
vigilance and behaviour  
*Drugs* 1983, 25 (Suppl 2) 278-79
- 36 CUSI D, VELIS O, VALLAR G, BERTONI T and  
BIANCHI G  
Neuropsychological side-effects of antihypertensive  
treatment.  
*J Hypertension* 1983, 1 (Suppl 2) 319-21
- 37 CLAYTON AB, HARVEY PG and BETTS TA.  
The psychomotor effects of atenolol and other  
antihypertensive agents  
*Postgrad Med J* 1977, 53 (Suppl 3) 157-61
- 38 LANDAUER AA, POCOCK DA and PROTTF FW  
Effects of atenolol and propranolol on human  
performance and subjective feelings  
*Psychopharmacology* 1979; 60 211-15
- 40 HARVEY PG, CLAYTON AB and BETTS TA.  
The effects of four antihypertensive agents on the  
Stroop colour-word test in normal male volunteer  
subjects  
*Psychopharmacology* 1977, 54 133-38

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**'Tenormin'**  
**in hypertension**

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## The increasing role of beta-blockade

Since the first report of an antihypertensive effect by [illegible] in 1964, beta-adrenergic blocking agents have become one of the most widely used classes of antihypertensive drugs. This is due to their effectiveness, safety, and the fact that they can be taken once daily.

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### Some general advantages of beta-blockers in hypertension

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- Evidence for a cardioprotective effect of beta-blockade additional to that of blood pressure control.<sup>3</sup>
- Effective in most grades of hypertension, races and age groups.
- Well tolerated compared with other antihypertensives and with a low incidence of side effects.<sup>3</sup>
- Good patient compliance, especially with beta-blockers which can be taken once daily.

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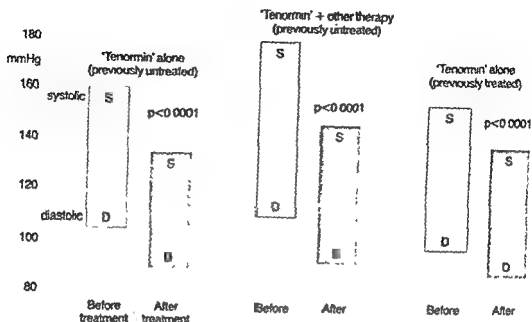
### 'Tenormin' – proven antihypertensive efficacy

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[Illegible text describing the efficacy of Tenormin in clinical trials]

Hg after treatment with 'Tenormin'.

**Figure 1. Effect of 'Tenormin' on blood pressure**



## **'Tenormin' compares favourably with other beta-blockers**

In 37 published comparative trials of 'Tenormin' monotherapy against other beta-blockers, most comparisons of blood pressure reduction were favourable to 'Tenormin', and it may be concluded that *'Tenormin' is at least as effective as other available beta-blockers in short-term blood pressure reduction, and more effective than most others 20-24 hours after dosing*<sup>6-48</sup> (Figures 2 and 3).

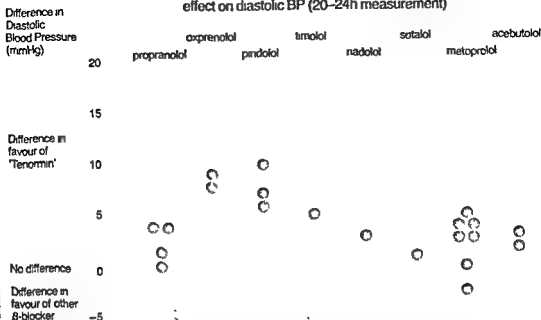
## **Efficacy and tolerance compared with other antihypertensives**

### **Comparison with diuretics**

'Tenormin' has been shown in several studies to be more effective than a thiazide diuretic in lowering blood pressure.<sup>9,45-48</sup>

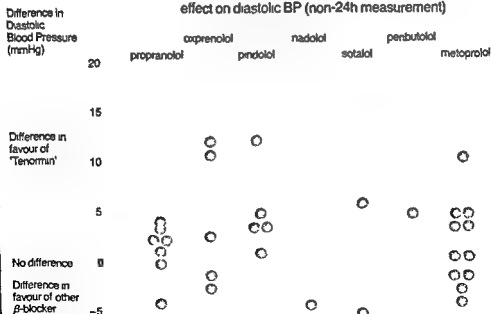
There is a growing body of evidence that long-term diuretic monotherapy for hypertension may cause

**Figure 2. Randomised controlled studies of 'Tenormin' vs. other  $\beta$ -blockers. Difference in effect on diastolic BP (20-24h measurement)**



References 8, 10, 13-16, 20, 22, 24, 25, 29, 30, 40, 78

**Figure 3. Randomised controlled studies of 'Tenormin' vs. other  $\beta$ -blockers. Difference in effect on diastolic BP (non-24h measurement)**



References 6, 7, 9, 12, 13, 15, 17, 20, 22, 23, 26, 27, 29, 31-36, 38, 39, 41-44



significant problems including hypokalaemia, an

Professor Dollery has commented that *"The available evidence suggests that beta-blockers are a*

*beneficial one . . . Beta-adrenoceptor-blocking drugs appear to have the balance of advantage over thiazide diuretics as the first choice when treatment is initiated."*<sup>52</sup>

Indeed, concluded from his

*disturbance, decreased frequency of complaints and*

is discussed later in the present chapter

## Comparison with methyldopa

improved blood pressure control with 'Tenormin' as compared with methyldopa, again with a lower incidence of reported problems.<sup>61,62</sup>

Indeed, Magnani concluded from his double-blind randomised comparison that the *" . . . antihypertensive activity of Tenormin' 100mg once daily does not*

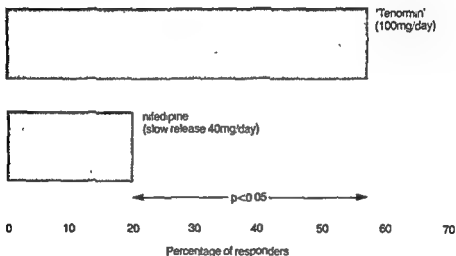
## Comparison with nifedipine

Therapeutic trial data available on the use of nifedipine

A double-blind crossover study of 35 patients by Daniels and Opie<sup>66</sup> showed that for initial therapy in mild to moderate hypertension, 'Tenormin' was significantly more effective than nifedipine as monotherapy (Figure

which may be of particular benefit to patients with resistant hypertension.

Figure 4. Supine diastolic pressure reduced to less than 90mm Hg with monotherapy (n=35)

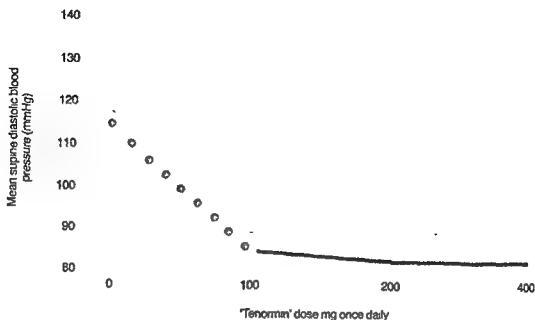


## Advantages of 'Tenormin' in clinical practice

### Flat dose-response curve

dose in moderate and established hypertension. Doses in excess of 100mg/day rarely, if ever, give further benefit.<sup>69</sup>

**Figure 5. The dose-response curve for 'Tenormin' (n = 16)**



### **Rapid onset of action**

'Tenormin' is effective in severe hypertension within 12 hours of the first dose,<sup>71</sup> and some reduction in diastolic blood pressure within 2-3 hours of taking a single 100mg tablet has been reported.<sup>72</sup> Fagard found that the major effect was obtained within 48 hours, in contrast to the delay with thiazide diuretics.<sup>45</sup> Thus the effectiveness of 'Tenormin' builds up rapidly at first, but approaches a maximum more gradually thereafter.

### **One-tablet-daily dosing**

The long half-life of 'Tenormin' and consequent smooth control throughout 24 hours are discussed fully in the 'Pharmacokinetics' chapter.

Several investigators have confirmed that 'Tenormin' remains effective in hypertension after several years of continuous use.<sup>4,73,74</sup>

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## Efficacy

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The worldwide use of 'Tenormin' now extends to over 40 countries and over 1000

### The elderly

'Tenormin', alone or in combination, is effective and well tolerated in elderly patients. A separate section later in the chapter deals with this aspect.

### Renin levels

It has been suggested that beta-blocker monotherapy

give consistent support to a connection

### Race

There is considerable evidence of the effectiveness of

more effective. A combination of these drugs produced an even greater reduction.

It may be that a beta-blocker/diuretic combination is most suitable for black hypertensives because the diuretic eliminates excess plasma volume or sodium concentration, allowing the beta-blocker to act more effectively.<sup>76,78</sup>

There is considerable evidence of the effectiveness of 'Tenormin' in hypertensive Asians.<sup>59,60,79-81</sup>

### Asthmatics

There is no evidence of any adverse effects on

### Diabetics

The cardioselective properties of 'Tenormin' make it an appropriate choice of beta-blocker for diabetics at risk of hypoglycaemia (see also 'Cardioselectivity' chapter)

### Cigarette smoking and coffee drinking

The consumption of coffee and cigarettes has

'Cardioselectivity' chapter)

## Combinations with other antihypertensives

Patients may be transferred to 'Tenormin' directly from

other antihypertensive therapy, or may be added to existing therapy.

The combination of 'Tenormin' and a diuretic is well balanced for

added response, and free combinations with diuretics or calcium

antagonists (eg nifedipine) may be prescribed.

A particular advantage of this combination is that some

of the biochemical alterations seen with diuretic

therapy are offset by the effects of 'Tenormin'.

Combined treatment with 'Tenormin' and a diuretic

is well balanced for added response.

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therapy are offset by the effects of 'Tenormin'.

Combined treatment with 'Tenormin' and a diuretic

is well balanced for added response.

**'Tenoretic' = 'Tenormin' plus diuretic – well balanced for added response**

compliance

'Tenoretic' containing 100mg 'Tenormin' and 25mg

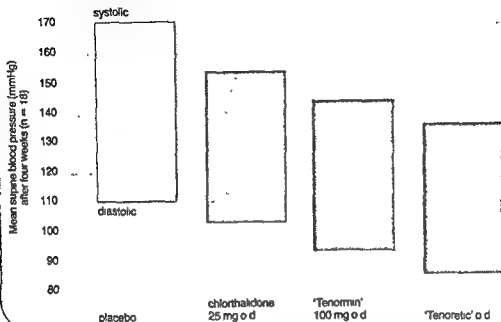
diuretic, is well balanced for added response.

A particular advantage of this combination is that some

of the biochemical alterations seen with diuretic

therapy are offset by the effects of 'Tenormin'.

**Figure 6. Evaluation of 'Tenormin', chlorthalidone and their combination, 'Tenoretic'**



In clinical trials, 'Tenoretic' produced diastolic blood pressures of 95mm Hg or less in about 75% of the patient population<sup>88</sup> There was a low incidence of side-effects<sup>89,90</sup> and the one-tablet-daily regime improved compliance<sup>91</sup>

*A meta-analytic evaluation of 'Tenoretic' in 6 510*

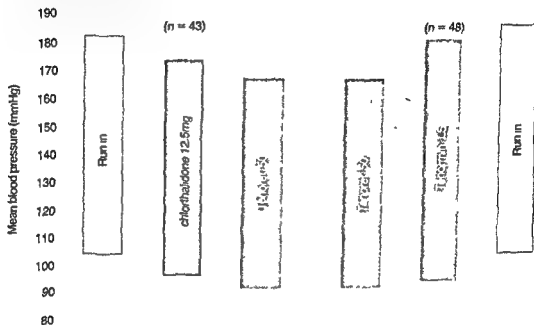
incidence of side-effects, particularly those related to the central nervous system

**'Tenoret' 50 –  
a low-dose combination  
for hypertension  
in the elderly**

'Tenoret' 50 is the first beta-blocker product to be

patients who are susceptible to side-effects on other therapy or who require simplification of their treatment.

**Figure 7. Effect of 'Tenoret' 50 on blood pressure of elderly hypertensive patients**



Blood pressure measurements taken at least 24 hours after the last dose

**'Tenormin' in  
combination with  
vasodilators and  
diuretics**

therapy is therefore especially crucial

Diuretics, dihydropyridine and peripheral vasodilators have

Hydralazine was the most generally suitable, with prazosin a close second choice. Methyldopa was similarly effective but less well tolerated. Minoxidil was more effective, but caused fluid retention in more severely hypertensive patients. Labetalol (500-7200 mg/





development being affected is a concern, nevertheless, there has been no report to date implicating 'Tenormin' in fetal malformation

'Tenormin' has been detected in both maternal and fetal plasma, indicating transplacental passage of the

rate when administered to patients for hypertension of pregnancy<sup>134,135</sup>

Rubin<sup>136</sup> stated in a review: *"The overall conclusion to*

## 'Tenormin' in hypertension of pregnancy

It has been stated that hypertension of pregnancy is not

with any medication used during pregnancy or lactation, the anticipated benefits of 'Tenormin' must be weighed against possible risks.

Rubin *et al*<sup>134</sup> conducted a placebo-controlled study comparing 'Tenormin' with conventional obstetric management in 120 women developing hypertension in the last trimester

'Tenormin' (100-200mg once daily) significantly reduced blood pressure, tended to prevent proteinuria, and reduced the need for hospital admissions. Conventional

'Tenormin' but the systolic blood pressure of the babies was the same in both groups. No baby died or had any congenital malformation

## Conclusions

The overall conclusions of this and other studies may be summarised as follows. 'Tenormin'.—

- Reduces maternal blood pressure effectively with a low incidence of side-effects <sup>134,135,137-142</sup>
- Reduces hospital admissions, with its consequent disruption of family life and expense <sup>134</sup>
- Reduces the incidence of mother-fetus distress
- Reduces the incidence of proteinuria, without masking the presence of this useful sign of fetal distress <sup>134</sup>
- Protects the placenta <sup>133 138 143</sup> to minimise maternal effects to the fetus.
- Accumulates in breast milk (about three times higher compared with maternal blood) <sup>139,143,144</sup>  
No detrimental effect in breast-fed babies has been reported. <sup>144</sup>
- No consistent effect on fetal heart rate <sup>134,135,141,145</sup> and no fall in neonatal blood pressure.

In summary, 'Tenormin' has been used under close supervision for the treatment of hypertension in pregnancy. It has been shown to be effective and no adverse effects on the fetus have been reported.

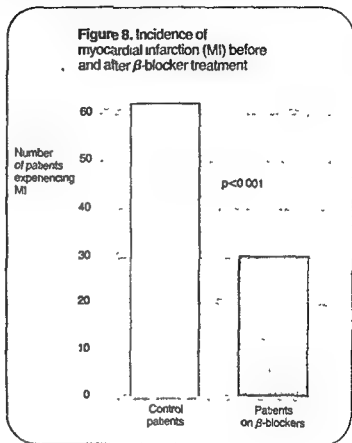
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## Cardioprotection with beta-blockers

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The reduction in mortality associated with beta-blockade during and after myocardial infarction is now well established

**Study 1** Patients hospitalised with prolonged ischaemic pain were divided into two groups of 90 each, those who had received a beta-blocker up to the time of admission and a matched sample who had not. Myocardial infarction was confirmed in 30 patients on beta-blockers and in 62 controls ( $p<0.001$ ) (Figure 8) <sup>146</sup>

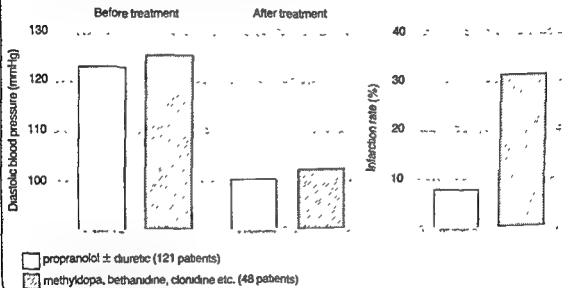


infarction were similar.

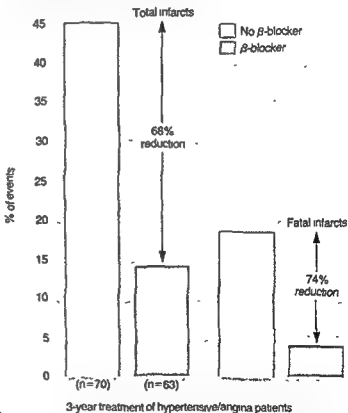
A similar reduction in blood pressure was achieved in

( $p < 0.01$ ) (Figure 9)

**Figure 9. Treatment of hypertension – effect upon occurrence of myocardial infarction (follow-up time up to 5½ years – mean = 2½ years)**



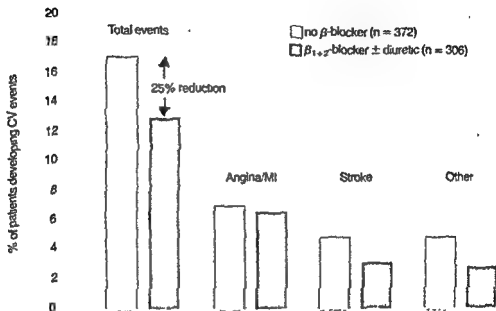
**Figure 10. Incidence of myocardial infarctions in 217 patients with angina with or without hypertension**



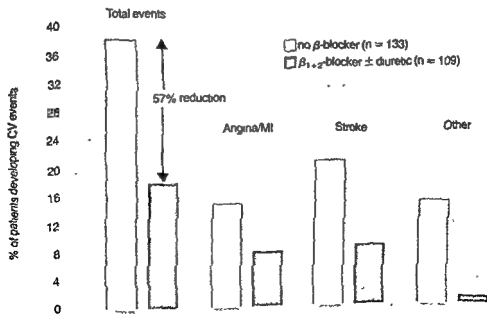
**Study 4** The results of treatment in 416 hypertensives who had received a beta-blocker for at least 3 years

**Figure 11. Incidence of cardiovascular (CV) complications in hypertensive patients**

First CV complication in 678 hypertensive patients



Second CV complication in 242 hypertensive patients



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## Does beta-blockade improve prognosis?

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The trial as described suggests that beta-blockade may

be superior to other antihypertensive therapy in the elderly, but it is not possible to distinguish between the cardioprotective efficacy of different beta-blockers in uncomplicated hypertension.

It is not possible to distinguish between the cardioprotective efficacy of different beta-blockers in uncomplicated hypertension.

### Summary: 'Tenormin' in hypertension

- Proven efficacy in many well-controlled trials
- Low incidence of side-effects in a wide range of patients
- Effective in all races
- Effective in all adult age groups
- Available in strengths and combinations for all grades of hypertension
- Effective in lowering diastolic, systolic and combined.
- Simple one-tablet-daily dosage regime
- Specifically demonstrated to be effective in the elderly with minimal side-effects
- May give a cardioprotective effect not seen with other types of antihypertensive therapy



# References

- 1 WAAL-MANNING JH  
Hypertension: Which beta-blocker?  
*Drugs* 1976, 12: 412-41
- 2 BUEHLER FR  
The antihypertensive drug of first choice  
In: Gross F, ed. The cardioprotective action of  
beta-blockers  
Bern/Stuttgart/Vienna: Hans Huber, 1977: 42-45
- 3 MEIER M, ORWIN J, ROGG M AND  
BRUNNER H  
.....
- 4 ZACHARIAS FJ, CUTHBERTSON PJR,  
PREST J et al  
Atenolol in hypertension: a study of long-term  
therapy  
*Postgrad Med J* 1977, 53 (Suppl 3): 102-10
- 5 HENNINGSEN NC  
9 years' experience with atenolol in the treatment  
of hypertension  
*Drugs* 1983, 25 (Suppl 2): 74-75
- 6 ZACHARIAS FJ  
Comparison of propranolol and atenolol in  
hypertension  
*Postgrad Med J* 1977, 53 (Suppl 3): 111-13
- 7 EPSTEIN SE and LUBIM WF  
Effects of propranolol and atenolol on blood  
pressure and plasma renin activity in patients  
with moderate hypertension  
*S Afr Med J* 1977, 52: 875-79
- 8 WILCOX RG  
Randomised study of six beta blockers and a  
thiazide diuretic in essential hypertension  
*Br Med J* 1978, 2: 385-85
- 9 MITCHELL TA, WILSHIR R, REID B and  
PETRIE JC  
Atenolol and metoprolol in mild hypertension  
*Br Med J* 1978, 2: 1269-70
- 10 ENGLAND JD, HUA ASP and SHAW J  
Beta-adrenoreceptor blocking agents and lipid  
metabolism  
*Clin Sci Mol Med* 1978, 55, 323s-24s
- 11 LEFEN FHH, COENEN CHM,  
ZONDERLAND M and MASS AHJ  
Effects of cardioselective and nonselective beta  
blockade in dynamic exercise performance in  
mildly hypertensive men  
*Clin Pharmacol Ther* 1980, 28 (1): 12-21
- 12 TURNER AS, WATSON OF and  
BROCKLEHURST JE  
Efficacy of atenolol and oxprenolol in the  
treatment of arterial hypertension  
*Med J Aust* 1979, 1 (13): 625-26
- 13 VAN-ROOIJEN GJM, BOER P, DORHOUT-  
MESS EJ and GEYSKES GG  
Effects of atenolol and propranolol when added  
to long-term antihypertensive diuretic therapy  
*Clin Pharmacol Ther* 1979, 26 (4): 420-27
- 14 LEARY WP, ASMALAC, BRAYSHAW P and  
WILLIAMS P  
Antihypertensive effects of sotalol and atenolol  
given once-daily  
*S Afr Med J* 1980, 57 (17): 692-95
- 15 PETRIE JC, JEFFERS TA, ROBB OJ, SCOTT AK  
and WEBSTER J  
Atenolol, sustained-release oxprenolol, and long  
acting propranolol in hypertension  
*Br Med J* 1980, 280 (6231): 1573-74
- 16 WILKINSON R, STEVENS IM, PICKERING M et al  
A study of the effects of atenolol and propranolol  
on renal function in patients with essential  
hypertension  
*Br J Clin Pharmacol* 1980, 10: 51-59
- 17 TURNER AS and BROCKLEHURST JE  
Efficacy of a single daily dose of acebutolol and  
atenolol in the treatment of arterial hypertension  
— a comparison  
*NZ Med J* 1980, 91 (659): 361
- 18 ADAMS-STRUMP BJ, HAYES J and BARBER JH  
A new approach to drug trials in general practice  
*Practitioner* 1980, 224: 541-44
- 19 LYNGSTAM O and RYDEN L  
Metoprolol and atenolol administered once-daily  
in primary hypertension  
*Acta Med Scand* 1981, 209: 261-66
- 20 MORLEY C, CAVALCANTI C, PERRINS J and  
SUTTON R  
Control of mild to moderate hypertension at rest  
and on exercise with single dose cardioselective  
beta blockade  
Eighth Scientific Meeting of the International  
Society of Hypertension, 31st May - 3rd June  
1981, Milan: Abstract 303

- 23 LION FM and TOPOROVSKI B  
A comparative study of the action of metoprolol and atenolol in once-daily dose, in the treatment of arterial hypertension  
*Rev Bras Med* 1981; 38 (8) 11-13
- 24 RASMUSSEN S, ARNUNG K, ESKILDSSEN PC and NIELSEN PE  
A comparative study of atenolol and metoprolol in the treatment of hypertension  
*Br J Clin Pharmacol* 1981; 12: 887-91
- 25 WILCOX RG and HAMPTON JR.  
Comparative study of atenolol, metoprolol, metoprolol durules and slow-release oxprenolol in essential hypertension  
*Br Heart J* 1981; 46: 498-502.
- 26 LAMEIJER LDF, VOERMANS LAGA,  
"  
"
- 27 DAY JL, METCALFE J and SIMPSON CN  
Adrenergic mechanisms in control of plasma lipid concentrations  
*Br Med J* 1982; 284: 1145-48
- 28 DAY JL, METCALFE J and SIMPSON CN  
Adrenergic mechanisms in the control of plasma lipids I, man  
In Noseda G et al, eds. Lipoproteins and coronary atherosclerosis  
Amsterdam Elsevier Biomedical Press BV, 1982, 355-61
- 29 SCOTT AK, RIGBY JW, WEBSTER J, HAWKSWORTH GM, PETRIE JC and LOVELL HG  
Atenolol and metoprolol once daily in hypertension  
*Br Med J* 1982; 284, 1514-16
- 30 WILCOX RG and HAMPTON JR.  
Comparison between atenolol and nadolol in essential hypertension at rest and on exercise  
*Br J Clin Pharmacol* 1982; 13: 841-46
- 31 ROSSNER B and WEINER L.  
A comparison of the effects of atenolol and metoprolol and serum lipoproteins  
*Drugs* 1983; 25 (Suppl 2) 322-25
- 32 NUKADAT  
Poster presented at a symposium "Beta-blockade in the 1980's - Focus on atenolol", June, 1982, Monte Carlo  
--  
.. .. .  
during exercise  
*Drugs* 1983; 25 (Suppl 2) 30-36
- 34 GREIMING P, VETTER H, BOERLIN HJ et al  
A comparative study between 100mg atenolol and 20mg pindolol slow-release in essential hypertension  
*Drugs* 1983; 25 (Suppl 2) 37-41  
^        ^        ^        ^
- oxprenolol  
*Curr Ther Res* 1982; 32 (1) 99-105
- 36 LAWRENCE DS, SAHAY JN, CHATTERJEE SS and CRUICKSHANK JM  
Asthma and beta-blockers  
*Eur J Clin Pharmacol* 1982; 22: 501-509
- 37 SALONEN JT and PALMINTERI R.  
Long-term treatment of hypertension with fixed doses of betaxolol or atenolol  
Presented at a symposium of the International Society and Federation of Cardiologists, Nov 7-14, 1982, Israel  
"  
"
- oxprenolol;  
*Curr Ther Res* 1982; 32 (6) 810-21
- 39 KJELSDSEN SE, EIDE I, LEREN P and FOSS OP  
Effect on high density lipoprotein cholesterol of atenolol and oxprenolol in patients with mild essential hypertension  
*Clin Sci* 1982; 63: 463s-65s
- 40 DOUGLAS-JONES AP and TWEED JA  
Randomised trial of two beta blocker/diuretic combinations (atenolol/chlorthalidone and pindolol/cloparamide) in mild to moderate hypertension  
*Acta Ther* 1982; 8: 345-51
- 41 FLORAS JS, JONES JV, HASSAN MO and SLEIGHT P  
Ambulatory blood pressure during once daily randomised double-blind administration of atenolol, metoprolol, pindolol and slow-release propranolol  
*Br Med J* 1982; 285: 1387-92
- 42 TRAFFORD JAP, MCGONIGLE R, BOWLES J et al  
A two year clinical evaluation of atenolol and metoprolol in the treatment of hypertension  
*Br J Clin Pract* 1982; 36 (10) 350-352
- 43 AARYNEN M, MAKELA M, HAMEENAHO P and MATTHILA MJ  
Prazosin enhances the antihypertensive effects of beta-blockers during isometric and dynamic exercise  
*Ann Clin Res* 1981; 13: 71-76

# References

- 1 WAAL-MANNING JH  
Hypertension: Which beta-blocker?  
*Drugs* 1976, 12: 412-41
- 2 BUHLER FR  
The antihypertensive drug of first choice  
In Gross F, ed. *The cardioprotective action of beta blockers*  
Bern/Stuttgart/Vienna: Hans Huber, 1977: 42-45
- 3 MEIER M, ORWIN J, ROGG M and BRUNNER H  
 $\beta$ -adrenoceptor antagonists in hypertension  
In Schnabbe A, ed. *Pharmacology of antihypertensive drugs*  
New York: Raven Press, 1980: 179-93
- 4 ZACHARIAS FJ, CUTHBERTSON PJR, PREST J *et al*  
Atenolol in hypertension: a study of long-term therapy  
*Postgrad Med J* 1977, 53 (Suppl 3): 102-10
- 5 HENNINGSEN NC  
9 years' experience with atenolol in the treatment of hypertension  
*Drugs* 1983, 25 (Suppl 2): 74-75
- 6 ZACHARIAS FJ  
Comparison of propranolol and atenolol in hypertension  
*Postgrad Med J* 1977, 53 (Suppl 3): 111-13
- 7 EPSTEIN SE and LUBBE WF  
Effects of propranolol and atenolol on blood pressure and plasma renin activity in patients with moderate hypertension  
*S Afr Med J* 1977, 52: 875-79
- 8 WILCOX RG  
Randomised study of six beta blockers and a thiazide diuretic in essential hypertension  
*Br Med J* 1978, 2: 383-85
- 9 JEFFERS TA, WILKINSON J, RICHARDSON B and PETRIE JC  
Atenolol and metoprolol in mild hypertension  
*Br Med J* 1978, 2: 1269-70
- 10 ENGLAND JDF, HUA ASP and SHAW J  
Beta-adrenoceptor blocking agents and lipid metabolism  
*Clin Sci Mol Med* 1978, 55: 323s-24s
- 11 LEENEN FHH, COENEN CHM, ZONDERLAND M and MASS AHJ  
Effects of cardioselective and nonselective beta-blockade in dynamic exercise performance in mildly hypertensive men  
*Clin Pharmacol Ther* 1980, 28 (1): 12-21
- 12 TURNER AS, WATSON OF and BROCKLEHURST JE  
Efficacy of atenolol and oxprenolol in the treatment of arterial hypertension  
*Med J Aust* 1979, 1 (13): 625-26
- 13 VAN-ROOIJEN GJM, BOER P, DORHOUT-MESS EJ and GEYSKES GG  
Effects of atenolol and propranolol when added to long-term antihypertensive diuretic therapy  
*Clin Pharmacol Ther* 1979, 26 (4): 420-27
- 14 LEARY WP, ASMAL AC, BRAYSHAW P and WILLIAMS P  
Antihypertensive effects of sotalol and atenolol given once-daily  
*S Afr Med J* 1980, 57 (17): 692-95
- 15 PETRIE JC, JEFFERS TA, ROBB OJ, SCOTT AK and WEBSTER J  
hypertension  
*Br J Clin Pharmacol* 1980, 10: 51-59
- 16 — a comparison  
*NZ Med J* 1980, 91 (659): 361
- 17 ADAMS-STRUMP BJ, HAYES J and BARBER JH  
A new approach to drug trials in general practice  
*Practitioner* 1980, 224: 541-44
- 18 COMERFORD MB and BESTERMAN H  
Dosing intervals in beta-blocker therapy  
*Lancet* 1980, 2 (8205): 1196
- 19 LYNSTAM O and RYDEN L  
Metoprolol and atenolol administered once-daily in primary hypertension  
*Acta Med Scand* 1981, 209: 261-66
- 20 MORLEY C, CAVALCANTI C, PERRINS J and SUTTON R  
Control of mild to moderate hypertension at rest and on exercise with single dose cardioselective

- 66 DANIELS AR and OPIE LH.  
Atenolol plus nifedipine for mild to moderate systemic hypertension after fixed doses of either agent alone.  
*Am J Cardiol* 1986, 57, 965-70
- 67 ZACHARIAS FJ, HAYES PJ and CRUICKSHANK JM  
Atenolol in hypertension: a double-blind comparison of the response to three different doses  
*Postgrad Med J* 1977, 53 (Suppl 3) 114-15
- 70 TARAZI RC and DUSTAN MP  
Beta adrenergic blockade in hypertension  
*Am J Cardiol* 1972, 29, 633-40
- 71 BANNAN LT and BEEVERS DG  
Single dose oral atenolol for urgent blood pressure reduction  
*Drugs* 1983, 25 (Suppl 2) 23
- 73 COREA L, BENTIVOGLIO M, COSMI F, MILLA U, PROVIDENZA M  
Antihypertensive effect at rest and during isometric exercise of long-term treatment with atenolol  
*Drugs* 1983, 25 (Suppl 2) 76-77
- 75 HUMPHREYS GS and DELVIN DG  
Ineffectiveness of propranolol in hypertensive Jamaicans.  
*Br Med J* 1968, 2, 601-603
- 76 SEEDAT YK  
Trial of atenolol and chlorthalidone for hypertension in black South Africans  
*Br Med J* 1980, 2, 1241-43
- 77 POULTER N, SANDERSON JE, SEVER PS and OBELA A  
Comparative efficacy of first line drugs in the treatment of hypertension in the black African population  
*Acta Ther* 1978, 4: 255-66
- 78 GRELL GAC, ALLEYNE GAO, ROBINSON HM and ANDERSON M  
Treatment of Jamaican hypertensives with atenolol and chlorthalidone  
*West Indian Med J* 1981, 30 (3) 124-28
- 79 OH W and WEE A.  
The treatment of hypertension with single-daily doses of atenolol in Asians  
*Acta Ther* 1978, 4: 255-66
- 80 ZAINAL N and SHAHROM U  
Atenolol in the management of hypertension. Proceedings Ninth World Congress of Cardiology, 20-26 June, 1982, Moscow
- 81 ISHIZAKI T and OYAMA Y  
Atenolol dose-finding studies.  
*Drugs* 1983, 25 (Suppl 2) 42-49
- 82 LILJA A, JOUNELA AJ, JUUSTILA H] and PAALZOW L  
Abrupt and gradual change from clonidine to beta-blockers in hypertension  
*Acta Med Scand* 1982, 211: 375-80
- 83 BRAENDLI B, BUCHER HJ, NAGER F and TRUNIGER B  
Atenolol und Bendrofluzid in der Behandlung der mittelschweren und schweren Hypertonie  
*Schweiz Med Wochenschr* 1978, 108 (49) 1976-78
- 84 PITKAJARVI T  
Cyclothiazide and atenolol once-daily in essential hypertension  
*Ann Clin Res* 1979; 11: 1-8
- 85 NASH DT  
Concomitant atenolol and diuretic therapy in hypertension uncontrolled by diuretics alone.  
*Curr Ther Res* 1982, 32 (2) 196-201
- 86 MATERSON BJ, OSTER JR, MICHAEL UF *et al.*  
Dose response to chlorthalidone in patients with mild hypertension. Efficacy at a lower dose  
*Clin Pharmacol Ther* 1978, 24 192-98
- 87 TWEEDDALE MG, OGILVIE RI and RUEDY J  
Antihypertensive and biochemical effects of chlorthalidone  
*Clin Pharmacol Ther* 1977, 22: 519-27
- 88 ASBURY MJ, WELLS FO and BARKER NP  
Once daily combination therapy for hypertension  
*Practitioner* 1980, 224 (1350) 1306-309
- 89 SHERIFF MHR, HOWARD O and WARREN DJ  
Effects of atenolol, chlorthalidone and a new combined preparation. Tenoretic on blood pressure and total body potassium  
*Acta Ther* 1978, 4: 51-62
- 90 BATEMAN DN, DEAN CR, MUCKLOW JC, BULPITT CJ and DOLLERY CT  
Atenolol and chlorthalidone in combination for hypertension  
*Br J Clin Pharmacol* 1979, 7: 357-63

- 44 FRANZ IW and LOHMANN FW.  
Response of blood pressure under effort  
measured 2, 8 and 24 hourly following beta-  
blockers of different pharmacological  
characteristics, used in the chronic treatment of  
hypertension  
*Verh Dtsch Ges Inn Med* 1981, 87: 518-21
- 45 FAGARD R, AMERY A, DE PLAEN JF, LIJNEN  
P and MISSOTTEN A  
Relative value of beta-blockers and thiazides for  
initiating antihypertensive therapy  
*Acta Cardiol* 1976, 31 (5): 411-26
- 46 DOUGLAS-JONES AP and CRUICKSHANK JM  
Comparison of atenolol and bendrofluazide in  
mild to moderate hypertension  
*Acta Ther* 1976, 2: 221-34
- 47 PETRIE JC, GALLOWAY DB, WEBSTER J,  
SIMPSON WT and LEWIS JA  
Atenolol and bendrofluazide in hypertension  
*Br Med J* 1975, 4: 133-35
- 48 RUSHFORD WAI, TWEED JA and BARKER NP  
A comparison of atenolol and bendrofluazide in  
treating hypertension - a general practice study  
*Acta Ther* 1977, 3: 117-29
- 49 REICHGOTT MJ  
Problems of sexual function in patients with  
hypertension  
*Cardiovasc Med* 1979, 4 (2): 149-56
- 50 MEDICAL RESEARCH COUNCIL WORKING  
PARTY  
Adverse reactions to bendrofluazide and  
propranolol for the treatment of mild  
hypertension  
*Lancet* 1981, 2: 539-43
- 51
- 52 DOLLERY CT  
Does it matter how blood pressure is reduced?  
*Clin Sci* 1981, 61: 413s-20s
- 53 WILSON C, SCOTT ME and  
ABDEL-MOHSEN A  
Atenolol and methylodopa in the treatment of  
hypertension  
*Postgrad Med J* 1977, 53 (Suppl 3): 123-27
- 54
- 55 BASKER MA.  
Comparison of atenolol (Tenormin) and  
methylodopa (a multicentre study in general  
practice)  
*Proc R Soc Med* 1977, 70 (Suppl 15): 19-20
- 56 OKANGA JBO  
Atenolol (Tenormin) compared with methylodopa  
(Aldomet) in the treatment of hypertension.  
*East Afr Med J* 1978, 55 (9): 447-52
- 57 MAGNANI B, AMBROSIONI E, COSTA FV,  
MALINI PL and MAGELLI C.  
Comparison of antihypertensive activity of  
atenolol and methylodopa at rest and during  
exercise  
*Int J Clin Pharmacol Ther Toxicol* 1981, 19 (10):  
440-44
- 58 DE DIVITIIS O, PETITTO M, DISOMMA S  
and FAZIO S  
Atenolol and methylodopa in the treatment of  
mild-moderate hypertension - a double-blind  
comparison and combination with single doses.  
*Int J Clin Pharmacol Res* 1981, 1 (4): 245-53
- 59 PAU WI, LAI FK, CHENG F, LEE CP and  
SZETO ML  
Atenolol and methylodopa in hypertension  
*Proc Hong Kong Cardiol Soc* 1979, 6: 127-35
- 60 PAU WI, LAI FK *et al*  
Atenolol and methylodopa in hypertension  
Presented at the Asian Pacific Congress of  
Cardiology, Abstract 8 6, Bangkok.
- 61 TWEED JA, MASON B and SLEIGH R.  
Multicentre general practitioner assessment of  
Tenormin and methylodopa.  
*J Int Med Res* 1979, 7: 324-27
- 62
- 63 HUSTED SE, KRAEMMER NIELSEN M,  
CHRISTENSEN CK and LEDERBALLE  
PEDERSEN O  
Long term therapy of arterial hypertension with  
nifedipine given alone or in combination with a  
beta-adrenoceptor blocking agent.  
*Eur J Clin Pharmacol* 1982, 22: 101-103
- 64 LEWIS JG  
Adverse reactions to calcium antagonists  
*Drugs* 1983, 25: 196-222

moderate hypertension  
*Br Med J* 1977, 1: 76-78

Scand J Urol Nephrol 1984, 579: 93-97

hypertension

Acta Med Scand 1983, 213: 299-303

- 113 CALLENDER JS, HODSMAN GP, HUTCHESON MJ, LEVER AF and ROBERTSON JIS

Mood changes during captopril therapy for hypertension. A double-blind pilot study  
Hypertension 1983, 5 (3 Pt 2): III 90-III 93

- 114 PICKERING TG, CASE DB, SULLIVAN PA and LARAGH JH

Comparison of antihypertensive and hormonal effects of captopril and propranolol at rest and during exercise  
Am J Cardiol 1982, 49: 1566-68

- 115 STAESSEN J, FAGARD R, LIJNEN P, VERSCHUEREN LJ and AMERY A

Beta blockade during captopril treatment for hypertension  
N Engl J Med 1980, 303: 1121

- 116 FRITZ G, ABERG H, ASPLUND J et al

Erfarenheter med captopril ensamt eller i kombination med andra antihypertensiva läkemedel vid primär hypertoni  
Opusc Med 1982, 27: 55-60

- 117 HAMMOND JJ, KIRKENDALL WM and JACKS VL

Experience with captopril in the treatment of severe hypertension  
Pharmacologist 1979, 21: 177

- 118 SETO S, AOI W, DOI Y, MATSUMOTO A and HASHIBA K

Effect of captopril after propranolol in hypertensive man  
Proceedings of the Seventh Scientific Meeting of the International Society of Hypertension, Louisiana, 1980, (Abstract) 121

- 119 LEONETTI G, BIACHINI C, TERZOLI L et al

Acute hypotensive and renin-stimulating actions of captopril before and during treatment with a beta-blocking drug  
Am J Cardiol 1982, 49: 1564-65

- 120 HAVELKA J, BOERLIN HJ, STUDER A et al

Long-term experience with captopril in severe hypertension  
Br J Clin Pharmacol 1982, 14: 71s-76s

- 121 HUANG CM, SALOMON J, MOLTENI A, QUINTANILLA A and del GRECO F

Antihypertensive effect of captopril and propranolol  
Clin Pharmacol Ther 1980, 27: 258-59

- 122 LEDERLE RD, KLAUS D and BRAUN B

Captopril bei essentieller hypertonie  
Dtsch Med Wochenschr 1980, 105: 1307-12

- 123 FERGUSON RK, VLASSES PH, KOFFER H, CLEMENTI RA, KOPLIN JR and WILCOX CM

Effect of captopril and propranolol, alone and in combination, on the response to isometric and dynamic exercise in normotensive and hypertensive men  
Pharmacotherapy 1983, 3 (2 Pt 1): 125-30

- 124 STUMPE KO, KOLLOCH R and OVERLACK A

Reversible leucopenia associated with angiotensin-converting enzyme inhibitor MK-421  
Lancet 1982, 1: 458

- 125 BARNES JN, DAVIES ES and GENT CB

Rash, eosinophilia and hyperkalaemia associated with enalapril  
Lancet 1983, 2: 41-42

- 126 SAU F, CHERCHI A and SEGURO C

Reversal of left ventricular hypertrophy after treatment of hypertension by atenolol for one year  
Clin Sci 1982, 63: 367s-69s

- 127 COREA L, BENTIVOGLIO M and VERDECCHIA P

Echocardiographic left ventricular hypertrophy as related to arterial pressure and plasma norepinephrine concentration in arterial hypertension. Reversal by atenolol treatment  
Hypertension 1983, 5 (6): 837-43

- 128 IBRAHIM MM, MADKOUR MA and MOSSALLAM R

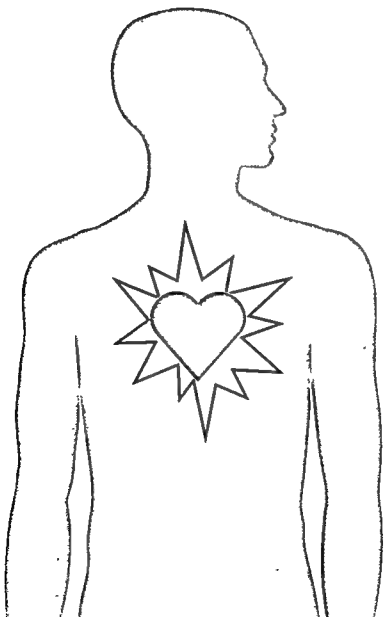
Factors influencing cardiac hypertrophy in hypertensive patients  
Clin Sci 1981, 61 (Suppl 7): 100s-100s

- 91 AZZOLINI A, CORAZZA M, GLANROSSI R, INTINI C, LIVI E and NIZZO MC  
A new beta-blocker (atenolol) and a diuretic (chlorthalidone) in combination for the treatment of hypertension  
*Curr Ther Res* 1981, 30 (5 Pt 2) 691-97
- 92 TWEED JA and EDWARDS KG  
Atenolol/chlorthalidone tablets in the management of hypertension in general practice  
A multicentre study  
*Acta Ther* 1984, 10: 15-22
- 93 BACKHOUSE CI, HOSIE J, TWEED JA and EDWARDS KG  
Atenolol and chlorthalidone in combination in the management of older hypertensive patients: a randomised clinical trial  
*Curr Med Res Opin* 1985, 9: 378-83
- 94 EDITORIAL  
Hypertension in the elderly  
*Lancet* 1977, 1: 684
- 95 SHURTFIELD D  
In Kannel WB and Gordon T, eds *The Framingham Study*  
Section 30, Dept of Health, Education and Welfare, 1974, Washington
- 96 WILCOX RG  
Combination hypotensive therapy with atenolol, bendrofluzide and hydralazine  
*Postgrad Med* 1977, 51 (Suppl 3) 128-33
- 97 WILCOX RG and MITCHELL JRA  
Contribution of atenolol, bendrofluzide and hydralazine to management of severe hypertension  
*Br Med J* 1977, 2, 547-50
- 98 DE DIVITIIS O, PETITTO M, DI SOMMA S, CAPUANO V and FAZIO S  
Atenolol and chlorthalidone in combination  
*Am J Cardiol* 1982, 50 (Suppl 3) 128-33
- 99 McAREAVEY D, RAMSAY LE, LATHAM L *et al*  
The 'third drug' trial: A comparative study of antihypertensive agents added to treatment when blood pressure is uncontrolled by a beta-blocker plus thiazide diuretic  
Presented at First European Meeting on Hypertension, May-June, 1983, Milan
- 100 LATHAM L, McAREAVEY D, RAMSAY LE and WILCOX RG  
Antihypertensive effect of atenolol and chlorthalidone in combination  
*Am Heart J* 1982, 104 (3) 606-12
- 101 LEDERBALLE PEDERSEN O, CHRISTENSEN CK, MIKKELSEN E and RAMSCH KD  
Relationship between the antihypertensive effect and steady-state plasma concentration of nifedipine given alone or in combination with a beta-adrenoceptor blocking agent  
*Eur J Clin Pharmacol* 1980, 18, 287-93
- 102 LATHAM L, McAREAVEY D, RAMSAY LE and WILCOX RG  
Antihypertensive effect of atenolol and chlorthalidone in combination  
*Am Heart J* 1982, 104 (3) 606-12
- 103 de BUITLEIR M, ROWLAND E and KRIKLER DM  
Hemodynamic effects of nifedipine given alone and in combination with atenolol in patients with impaired left ventricular function  
*Am J Cardiol* 1985, 55 15E-20E
- 104 KIEVAL J, KIRSTEN EB, KESSLER KM, MALLON SM and MYERBORG RJ  
The effects of intravenous verapamil on hemodynamic status of patients with coronary artery disease receiving propranolol  
*Circulation* 1982, 65 (4) 653-59
- 105 LIUJA M, JOUNELA AJ, JUUSTILA H and MATTILA MG  
Interaction of clonidine and beta-blockers  
*Acta Med Scand* 1980, 207, 173-76
- 106 ENALAPRIL IN HYPERTENSION STUDY GROUP  
Enalapril in essential hypertension: a comparative study with propranolol  
*Br J Clin Pharmacol* 1984, 18: 51-56
- 107 ENALAPRIL IN HYPERTENSION STUDY GROUP  
Enalapril in essential hypertension: a comparative study with propranolol  
*Br J Clin Pharmacol* 1984, 18: 51-56
- 108 WINER N and CARTER CH  
Effects of enalapril (MK-421) and metoprolol on blood pressure, converting-enzyme, renin and catecholamines  
*Clin Pharmacol Ther* 1983, 33: 232
- 109 ARR SM, BURGESS J, COOPER WD *et al*  
A comparative study of enalapril and atenolol in moderate to severe hypertension  
*Br J Clin Pharmacol* 1984, 18 (2) 267p
- 110 LICHTER I, RICHARDSON PJ and WYKE MA  
Differential effects of atenolol and enalapril on tests of memory during treatment for essential hypertension  
*J Hypertension* 1984, 2: 10

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**'Tenormin'**  
**in angina**

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132. NEUMAN CWG, BEILIN LJ and BONNAR J  
Treatment of hypertension in pregnancy with  
methyldopa: blood pressure control and side-  
effects  
*Br J Obstet Gynaecol* 1977, 84: 419-26
133. MCFARLANE J  
The use of beta-blockers in pregnancy  
*Br J Obstet Gynaecol* 1981, 88: 100-10
134. RUBIN PC, BUTTERS L, LOW DA and  
ADAMS D  
Atenolol in the treatment of hypertension of  
pregnancy  
*Drugs* 1983, 25 (Suppl 2): 206-11
135. RUBIN PC, BUTTERS L, LOW DA and  
ADAMS D  
Atenolol in the treatment of hypertension of  
pregnancy  
*Drugs* 1983, 25 (Suppl 2): 206-11
136. RUBIN PC  
Beta-blockers in pregnancy  
*N Engl J Med* 1981, 305: 1323-26
137. REYNOLDS B, BUTTERS L, LOW DA and  
ADAMS D  
Atenolol in the treatment of hypertension of  
pregnancy  
*Drugs* 1983, 25 (Suppl 2): 206-11
138. RUBIN PC, BUTTERS L, LOW DA and  
ADAMS D  
Atenolol in the treatment of hypertension of  
pregnancy  
*Drugs* 1983, 25 (Suppl 2): 206-11
139. LIEBHOLM H  
Atenolol in the treatment of hypertension of  
pregnancy  
*Drugs* 1983, 25 (Suppl 2): 206-11
140. DUBOIS D, PETTIT D, LAMBERT D  
and BEEVERS DG  
Clinical evidence that  $\beta$ -adrenoceptor blockers  
prevent more cardiovascular complications than  
other antihypertensive drugs  
*Drugs* 1983, 25 (Suppl 2): 326-30
141. RUBIN PC, BUTTERS L, CLARK D et al  
Obstetric aspects of the use of beta-blockers  
in pregnancy  
*Br J Obstet Gynaecol* 1984, 91: 117-19
142. AUREAU X, COLLET M, BEEVERS DG  
and LAMBERT D  
Clinical evidence that  $\beta$ -adrenoceptor blockers  
prevent more cardiovascular complications than  
other antihypertensive drugs  
*Drugs* 1983, 25 (Suppl 2): 326-30
143. RUBIN PC, BUTTERS L, CLARK D et al  
Obstetric aspects of the use of beta-blockers  
in pregnancy  
*Br J Obstet Gynaecol* 1984, 91: 117-19
144. RUBIN PC, BUTTERS L, CLARK D et al  
Obstetric aspects of the use of beta-blockers  
in pregnancy  
*Br J Obstet Gynaecol* 1984, 91: 117-19
145. INGRAM D, RUBIN PC, BUTTERS L, CLARK D  
et al  
Obstetric aspects of the use of beta-blockers  
in pregnancy  
*Br J Obstet Gynaecol* 1984, 91: 117-19
146. FOX KM, CHOPRA MP, PORTAL RW and  
ABER CP  
Long-term beta-blockade: Possible protection  
from myocardial infarction  
*Br Med J* 1975, 1: 117-19
147. RUBIN PC, BUTTERS L, CLARK D et al  
Obstetric aspects of the use of beta-blockers  
in pregnancy  
*Br J Obstet Gynaecol* 1984, 91: 117-19
148. LAMBERT D  
Clinical evidence that  $\beta$ -adrenoceptor blockers  
prevent more cardiovascular complications than  
other antihypertensive drugs  
*Drugs* 1983, 25 (Suppl 2): 326-30
149. BEEVERS DG, JOHNSTON JH, LARKIN H  
and DAVIES P  
Clinical evidence that  $\beta$ -adrenoceptor blockers  
prevent more cardiovascular complications than  
other antihypertensive drugs  
*Drugs* 1983, 25 (Suppl 2): 326-30

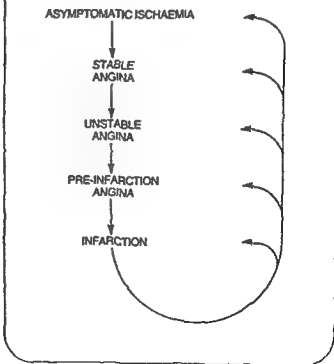
## Angina – a spectrum of clinical conditions

The supply of blood and oxygen to the heart is usually

discussed in more detail below).

Patients with angina may present with a spectrum of clinical conditions ranging from symptomless (silent) ischaemia along a continuum of worsening symptoms to the most severe form of ischaemia, myocardial infarction (Figure 1)

**Figure 1.**  
Ischaemic heart disease continuum



# Contents

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## Unstable angina

Unstable angina is a symptom complex about 15% of

platelet aggregates, thrombosis or vasospasm. The latter "functional ischaemia" can further complicate effort- or stress-induced angina<sup>10</sup> and S-T segment depression or

frequent, more prolonged or more severe; secondly,

Due to the plethora of terminology used for different

## Variant angina

Variant (Prinzmetal) angina occurs only in

and pain at rest.

---

## **'Tenormin' – a first-line therapy in stable angina**

---

### The action of 'Tenormin' in angina

Angina pectoris is a symptom complex resulting from a  
reduction in the myocardial blood flow to the heavily high

## Overall view

populations<sup>1-3</sup> Therefore control of symptoms at an early stage may protect against the consequences of disease progression

## Silent ischaemia

Asymptomatic or silent ischaemia is characterised by episodes of painless ischaemia (as detected by S-T

of MI or angina.<sup>6</sup>

The prevalence of silent ischaemia ranges from 2.5-10%,

less than one per cent per year in male office workers<sup>7</sup> and men with asymptomatic coronary disease without previous infarction<sup>9</sup> but is worse for patients with additional overt cardiovascular disease.<sup>6</sup>

## Stable angina

Stable angina is characterised by attacks of chest pain or discomfort which are precipitated by exertion or stress and which are relieved by rest. It is due to ischaemia due to a fixed coronary obstruction or to "functional ischaemia" of varying aetiology (see also below)<sup>10</sup> In the majority of cases, atherosclerosis is the cause.<sup>10</sup> Oxygen supply to the heart is

Stable angina is characterised by pain lasting only a few minutes and which is relieved by rest; S-T segment depression is usually evident

After the onset of uncomplicated angina, the condition may persist unchanged for varying periods, even for

## **'Tenormin' – effective beta-blockade in stable angina**

'Tenormin' has been compared with other beta-blockers

'Tenormin' was at least as effective as the other beta-blockers as measured by a reduction in anginal attacks, GTN consumption, and an improvement in S-T segment depression and exercise tolerance. In no case was another beta-blocker overall more effective than 'Tenormin'.

### **Comparison with beta-blockers with ISA**

Intrinsic sympathomimetic activity (ISA) refers to the ability of some beta-blockers to stimulate the heart at rest. 'Tenormin' does not have ISA (sometimes known as partial agonist activity or PAA)

sympathomimetic activity Pindolol was shown to

In therapeutic doses, 'Tenormin' did not increase ECG parameters of

In 19 rigorous studies (all placebo-controlled, double-blind and most of them randomised) including a total of over 360 patients and comparing 'Tenormin' with placebo, the overall results presented the same

ischaemia (S-T segment changes) were not significantly different.

'Tenormin' prove to have an overall detrimental effect on stable angina.

**Table 1. Anti-anginal efficacy of 'Tenormin' (100mg/day) compared with placebo**

Parameter	Percentage improvement*	References
Reduction in anginal attacks	51	21,23-30,32,33,36-38
Reduction in GTN consumption	46	21,23,29,32,33,36-38
Improvement in exercise capacity (workload or duration)	32	21,25,27,29,30,32,34,37
Improvement in exercise S-T changes:		21,24,25,28,
Severity (mm)	49	30-32,35,37,39
Area (no of positions)	54	25,26,31
Improvement in ambulatory S-T changes.		
Total number	53	25,26,30
Duration (minutes)	57	25,30

\*Average of values in studies cited expressed as a percentage

**Table 2. Comparison of 'Tenormin' with other beta-blockers**

'Tenormin' Dose	Comparator	Study Design (Duration/ weeks)	Anginal Attacks	Results		
				GTN Con- sumption	Exercise Tolerance	References
25, 50 100mg bd	propranolol 80mg tds	DB (4)	T=Pr	—	T=Pr	21
100, 200mg od 100mg bd	propranolol 160, 320mg/ day	DB (4)	T=Pr	T=Pr	T=Pr	50
100, 200mg od 100mg bd	propranolol 80mg bd	DB (3)	T*>Pr	T*>Pr	—	41
100mg od	propranolol 120-320mg/ day	SB (4)	T=Pr	T=Pr	T>Pr	51
100mg od	propranolol 240mg/day	DB (1)	T=Pr	—	T=Pr	25
100mg od	pindolol 5mg tds	CO (6) R	T>Pi	T>Pi	T>Pi	47
100mg od	pindolol 5mg tds	DB (5 days)	T>Pi	—	T>Pi	30
100mg/day	pindolol 20mg/day	DB (2)	T=Pi	T=Pi	—	52
100mg od	betaxolol 20mg od	DB (2)	T=B	T=B	T=B	24
100mg od	bisoprolol 10mg od	DB (3)	—	—	T>Bi	34
50, 100 200mg bd	practolol 100 200, 400mg bd	DB (2)	T>Pa	T>Pa	T=Pa	23

DB=double blind, SB=single blind, R=randomised, CO=cross over, T='Tenormin', Pr=propranolol, Pi=pindolol, Pa=practolol, B=betaxolol, Bi=bisoprolol, \*'Tenormin' 100mg bd

Both clinical trials highlighted the superior ability of 'Tenormin' to reduce heart rate at rest and during

During competitive cycling, a reduction of heart rate



**Figure 2. Anti-anginal efficacy in relation to dose of 'Tenormin' compared with placebo** 19,21-30,32 34,36-38,43,44,46-49

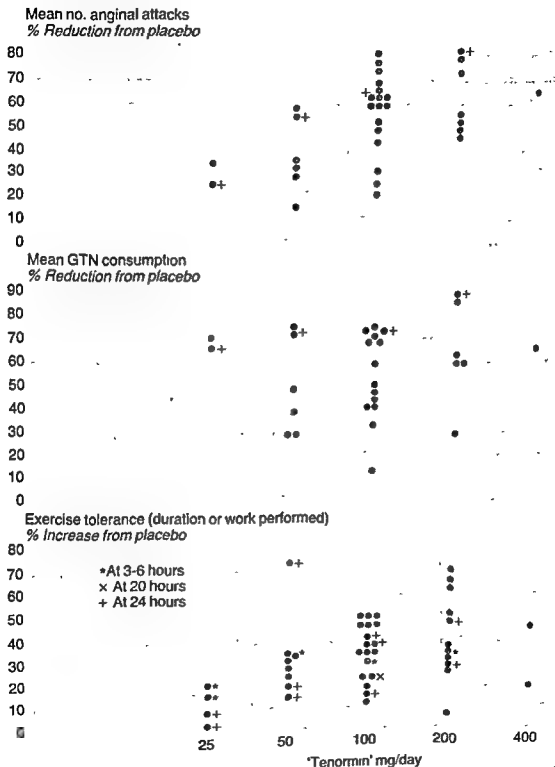


Table 2. Comparison of 'Tenormin' with other beta-blockers

'Tenormin' Dose	Comparator	Study Design (Duration/ weeks)	Anginal Attacks	Results		References
				GTN Con- sumption	Exercise Tolerance	
25, 50 100mg bd	propranolol 80mg tds	DB (4)	T=Pr	—	T=Pr	21
100, 200mg od 100mg bd	propranolol 160, 320mg/ day	DB (4)	T=Pr	T=Pr	T=Pr	50
100, 200mg od 100mg bd	propranolol 80mg bd	DB (3)	T*>Pr	T*>Pr	—	41
100mg od	propranolol 120-320mg/ day	SB (4)	T=Pr	T=Pr	T>Pr	51
100mg od	propranolol 240mg/day	DB (1)	T=Pr	—	T=Pr	25
100mg od	pindolol 5mg tds	CO (6) R	T>Pi	T>Pi	T>Pi	47
100mg od	pindolol 5mg tds	DB(5 days)	T>Pi	—	T>Pi	30
100mg/day	pindolol 20mg/day	DB (2)	T=Pi	T=Pi	—	52
100mg od	betaxolol 20mg od	DB (2)	T=B	T=B	T=B	24
100mg od	bisoprolol 10mg od	DB (3)	—	—	T>Bi	34
50, 100 200mg bd	practolol 100 200, 400mg bd	DB (2)	T>Pa	T>Pa	T=Pa	23

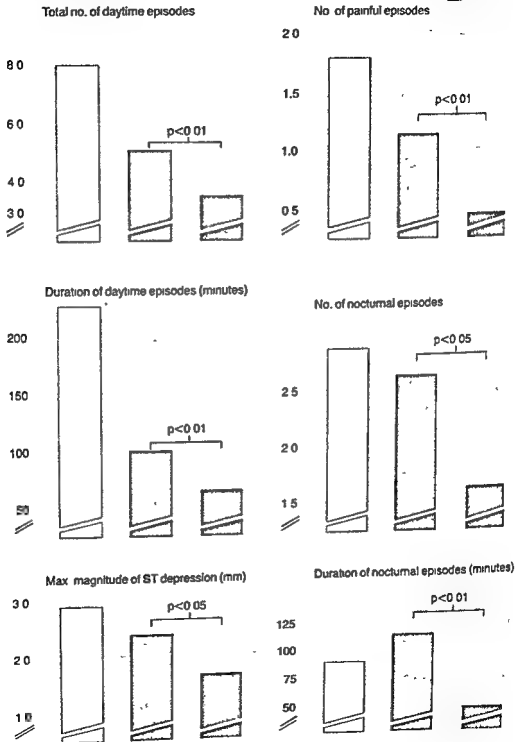
DB=double blind, SB=single blind, R=randomised, CO=cross over; T='Tenormin', Pr=propranolol, Pi=pindolol, Pa=practolol, B=betaxolol, Bi=bisoprolol, \*'Tenormin' 100mg bd

Both clinical trials highlighted the superior ability of 'Tenormin' to reduce heart rate at rest and during exercise and consequently, control angina symptoms more than pindolol<sup>30,47</sup>

Postoperative pooled analysis of randomised trials

**Figure 3. Frequency, magnitude and duration of ST segment depression before and after treatment**

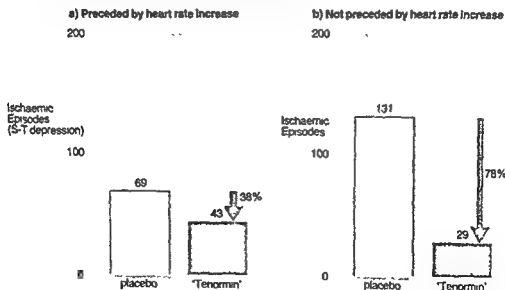
□ = run-in period  
 ▨ = pindolol  
 ▩ = "Tenormin"



also highly effective in cases of angina where ischaemia was caused by stimuli other than an increase in heart

episodes by 78% (Figure 4)<sup>60</sup> Other ischaemic periods were preceded by an increased heart rate, as other workers have also demonstrated<sup>30,61</sup> and in this group of patients, 'Tenormin' reduced the number of episodes by 38%<sup>60</sup> (Figure 4)

Figure 4. Effect of 'Tenormin' on ischaemia during daily activities (48 hour ambulatory monitoring)



## The importance of cardioselectivity

## The benefits of hydrophilicity

### The cardioselectivity of *Tenormin*

As discussed in the previous chapter, the cardioselectivity of *Tenormin* is an important feature of the drug. This is because it allows the drug to be used in patients with asthma and other respiratory conditions, which is a significant advantage over non-selective beta-blockers. The cardioselectivity of *Tenormin* is also important in patients with peripheral vascular disease, as it allows the drug to be used without the risk of exacerbating the condition.

### The hydrophilicity of *Tenormin*

The hydrophilicity of *Tenormin* is another important feature of the drug. This is because it allows the drug to be used in patients with renal impairment, which is a significant advantage over lipophilic beta-blockers. The hydrophilicity of *Tenormin* is also important in patients with heart failure, as it allows the drug to be used without the risk of exacerbating the condition.

*Tenormin* (100 mg od) has been compared with an equipotent beta-blocking dose of the lipophilic beta-blocker, *propranolol* (angina patients previously stabilised on long-term dosage of 120-320 mg/day in divided doses). *Tenormin* was at least as effective at this level, and significantly better when exercise capacity and ischaemic S-T changes were analysed.<sup>51</sup>

Other studies also indicated that *Tenormin* has similar efficacy to *propranolol* in angina.<sup>21,41,50</sup>

In a further double-blind, placebo-controlled study, *Tenormin* and *propranolol*, in equipotent doses, significantly reduced the number of cardiac attacks and

the need for medical intervention in patients with angina. The results are given later in this chapter.

Blood levels of *Tenormin* were unaffected by smoking, although the blood levels of *propranolol* were reduced.

## **'Tenormin' – a more effective first-line therapy than calcium antagonists in stable angina**

Two standard clinical methods of assessing the effects of treatment in patients with stable angina are exercise tolerance and the frequency of anginal attacks. In a double-blind study, 100 patients with stable angina were treated with either 'Tenormin' or verapamil. The results showed that 'Tenormin' and verapamil were equally effective in patients with stable angina<sup>33,35,64-68</sup> (Table 3)

### **Comparison with nifedipine**

In a double-blind study, 100 patients with stable angina were treated with either 'Tenormin' or nifedipine. The results showed that 'Tenormin' was more effective than nifedipine in controlling angina (Table 3)

During exercise testing in one of the studies, 'Tenormin' was found to be more effective than nifedipine in controlling angina (Table 3)

of pain, after 'Tenormin' than after nifedipine or placebo (Figure 7)<sup>25</sup> This study also compared 'Tenormin' with propranolol and the results are given earlier in this chapter

These trials showed that 'Tenormin' was more effective than nifedipine in controlling angina (Table 3)

### **Comparison with nifedipine in habitual smokers**

Two published trials comparing 'Tenormin' with nifedipine have included an investigation of the effects of smoking on angina therapy

The double-blind trial by Fox and colleagues<sup>25,62</sup> of

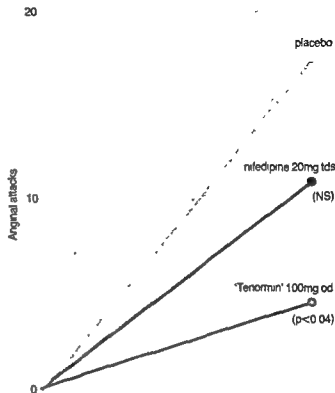
patients continued to smoke and received the drug treatments (including propranolol – see earlier in

**Table 3 Comparison of 'Tenormin' with calcium antagonists**

'Tenormin' Dose	Comparator	Study Design (Duration/ weeks)	Anginal Attacks	Results			References
				GTN Consumption	Improvement S-T changes	Exercise tolerance	
100mg od	nifedipine 10mg tds	DB (4)	T=N	T=N	—	T=N	■
100mg od	nifedipine 20mg tds, T+N	DB(3)	T>placebo N=placebo T+N>placebo	T>placebo N=placebo T+N>placebo	—	—	■
100mg od	nifedipine 60mg/day	DB (4)	T>N	—	—	T>N	■
100mg/day	nifedipine 20mg tds verapamil 120mg tds, T+N, T+V	DB (3)	—	—	T+N>placebo T>placebo N=placebo T+V>placebo V>placebo	—	35
100mg/day*	nifedipine 20mg tds*, 40mg bd(LA)*	DB (2)	variable response	—	—	variable response	63
100mg/day	nifedipine 20mg tds, verapamil 120mg tds, T+N, T+V	DB(2)	—	—	T=V T>N	—	64
100mg od	nifedipine 20mg tds, T+N	DB(3)	—	—	T+N>placebo T>placebo N=placebo	T+N>placebo T>placebo N=placebo	31
100mg/day	nifedipine 10-20mg tds, ISMN 40mg bd	DB (5 days)	T=N T>ISMN N=ISMN	—	T=N T>ISMN N=ISMN	T=N T>ISMN N=ISMN	61
100mg od*	nifedipine 20mg tds*, propranolol 160mg bd + nifedipine 20mg tds	R (2) CO	P+N=T+N	—	P+N=T+N	—	65
100mg/day	verapamil 120mg tds, T+V	R (6) CO	T+V>placebo T/V>placebo	T+V>placebo T/V>placebo	—	T+V>placebo T/V>placebo	68
50mg bd*	verapamil 120mg tds*, propranolol 80mg bd + verapamil 120mg tds	R (4) CO	T+V=P+V	T+V=P+V	—	—	66
100mg od	diltiazem 60mg tds	DB (6)	(T=D)> placebo	(T=D)> placebo	—	(T=D)> placebo	33
200mg/day	diltiazem 240mg/day	SB (2)	—	—	T>D	(T=D)> placebo	67
100mg od	nifedipine 30mg tds	DB(4)	T=Nic	—	T=Nic	T=Nic	■

T='Tenormin', N=nifedipine, V=verapamil, Nic=nicardipine, LA=long acting, \* = in combination, ISMN=isosorbide mononitrate, D=diltiazem, P=propranolol, DB=double blind, SB=single blind, R=randomised, CO=cross over

**Figure 5.**  
Mean number of anginal attacks during 3-week  
treatment periods



The investigators commented, "... atenolol ['Tenormin'] produced a significantly greater reduction than did nifedipine in the frequency of angina and the severity of ST-segment depression on the exercise test"<sup>25</sup>

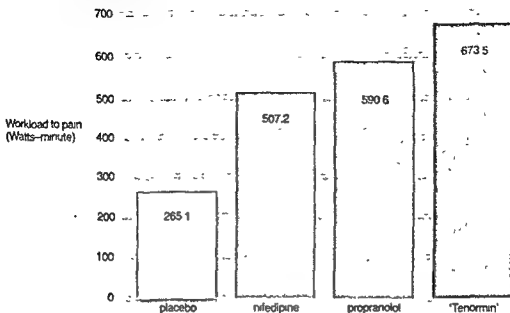


**Table 3 Comparison of 'Tenormin' with calcium antagonists**

'Tenormin' Dose	Comparator	Study Design (Duration/ weeks)	Anginal Attacks	Results			References
				GTN Consumption	Improvement S-T changes	Exercise tolerance	
100mg od	nifedipine 10mg tds	DB (4)	T=N	T=N	—	T=N	42
100mg od	nifedipine 20mg tds, T+N	DB(3)	T>placebo N=placebo T+N>placebo	T>placebo N=placebo T+N>placebo	—	—	38
100mg od	nifedipine 60mg/day	DB (4)	T>N	—	—	T>N	25
100mg/day	nifedipine 20mg tds, verapamil 120mg tds, T+N, T+V	DB (3)	—	—	T+N>placebo T>placebo N=placebo T+V>placebo V>placebo	—	35
100mg/day*	nifedipine 20mg tds*, 40mg bd(LA)*	DB (2)	variable response	—	—	variable response	63
100mg/day	nifedipine 20mg tds, verapamil 120mg tds, T+N, T+V	DB(2)	—	—	T=V T>N	—	64
100mg od	nifedipine 20mg tds, T+N	DB(3)	—	—	T+N>placebo T>placebo N>placebo	T+N>placebo T>placebo N=placebo	31
100mg/day	nifedipine 10-20mg tds, ISMN 40mg bd	DB (5 days)	T=N T>ISMN N=ISMN	—	T=N T>ISMN N=ISMN	T=N T>ISMN N=ISMN	61
100mg od*	nifedipine 20mg tds*, propranolol 160mg bd + nifedipine 20mg tds	R (2) CO	P+N=T+N	—	P+N=T+N	—	65
100mg/day	verapamil 120mg tds, T+V	R (6) CO	T+V>placebo T/V>placebo	T+V>placebo T/V>placebo	—	T+V>placebo T/V>placebo	68
50mg bd*	verapamil 120mg tds*, propranolol 80mg bd + verapamil 120mg tds	R (4) CO	T+V=P+V	T+V=P+V	—	—	66
100mg od	diltiazem 60mg tds	DB (6)	(T=D)> placebo	(T=D)> placebo	—	(T=D)> placebo	33
200mg/day	diltiazem 240mg/day	SB (2)	—	—	T>D	(T=D)> placebo	67
100mg od	nifedipine 30mg tds	DB(4)	T=Nic	—	T=Nic	T=Nic	69

T= 'Tenormin', N=nifedipine; V=verapamil, Nic=nifedipine, LA=long acting, \*=in combination, ISMN=isosorbide mononitrate, D=diltiazem, P= propranolol, DB=double blind, SB=single blind, R=randomised, CO=cross over

**Figure 7.**  
Workload to onset of chest pain with maximal exercise



In a further study, using higher doses of 'Tenormin' (200mg/day) and diltiazem (240mg/day), both drugs were equally effective in improving exercise tolerance (Table 3). Furthermore, 'Tenormin' produced significantly more improvement in S-T segment depression than diltiazem.<sup>67</sup> It was concluded that, "['Tenormin'] has greater anti-ischaemic activity than diltiazem."

## Comparison with nicardipine

There is no evidence has been presented that Tenormin is d

## Comparison with verapamil

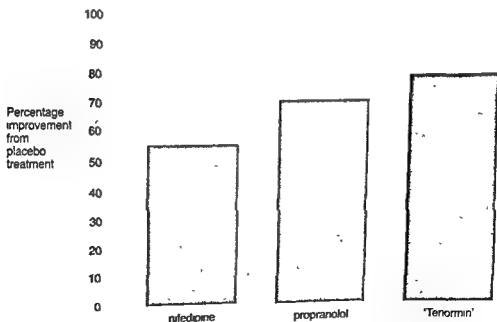
1 pccm68 assessed minomethazepam with verapamil (2gms

In a second study of 15 patients with stable angina pectoris, 'Tenormin' (100mg/day) and verapamil (120mg tds) significantly ameliorated exercise-induced S-T segment depression to an equal extent<sup>35,38</sup> (Table 3)

## Comparison with diltiazem

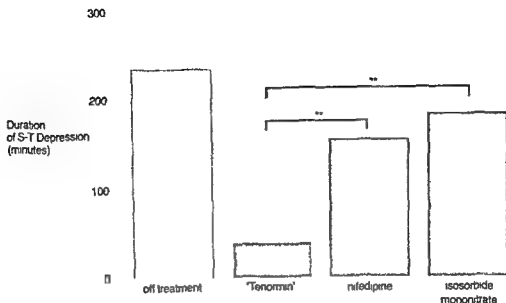
'Tenormin' (100mg od) and diltiazem (60mg tds) were between the two treatments.

Figure 6.  
Improvement in S-T segment depression in stable angina



**Figure 8.**  
Improvement in S-T segment depression  
in unstable angina

**\*\*p<0.01**



The investigators concluded "Overall, beta-receptor

blockade with atenolol was effective in the treatment of unstable angina. The combination of atenolol with calcium antagonists or other anti-anginal drugs was also effective. The combination of atenolol with calcium antagonists or other anti-anginal drugs was also effective. The combination of atenolol with calcium antagonists or other anti-anginal drugs was also effective.

patients became asymptomatic on 'Tenormin' alone and a further 27% responded to 'Tenormin' in combination with calcium antagonists and other anti-anginal drugs. The authors commented "The administration of atenolol ['Tenormin'] proved to be clinically efficient without left ventricular failure in two-thirds of the patients during hospitalisation and at mid-term follow-up"<sup>80</sup>

## More effective than pindolol

Fifteen patients were included in a double-blind, randomised comparison of 'Tenormin' with pindolol (see earlier section in this chapter)<sup>30</sup> About half of the patients had unstable angina occurring at rest and on effort and the remainder on effort alone. Analysis of all

## **'Tenormin' – an effective treatment in unstable angina**

*adrenergic blockade therapy if the latter does not appear to be immediately effective."*<sup>74</sup>

increase vascular resistance (due to unopposed  $\alpha$ -mediated vasoconstriction) and exacerbate spasm.<sup>79</sup>

### **Overall more effective than nifedipine and ISMN**

Newer evidence has demonstrated that 'Tenormin' is indicated in patients with severe angina occurring on effort and during the night and which may be the result of severe coronary artery disease.<sup>61</sup> In a double-blind, randomised, cross-over study, nine patients with this

ent  
were assessed by ambulatory ECG monitoring and exercise testing

spasm – however, beta-blocker treatment did not exacerbate his condition.<sup>61</sup>

ischaemic episodes was also reduced more by 'Tenormin' than either of the other two treatments (Figure 9).<sup>61</sup>

Few trials have compared 'Tenormin'/nifedipine with other beta-blocker/nifedipine combinations. 'Tenormin'/nifedipine was about as effective as other combinations<sup>65</sup>

## 'Tenormin'+verapamil

Monotherapy with verapamil (240mg daily) or

was significantly longer than on monotherapy ( $p<0.01$ ) and GTN consumption was significantly lower ( $p<0.01$ ) than baseline.

Other studies have confirmed that addition of verapamil to 'Tenormin' produces an additional reduction in S-T segment depression and provides good control of

particularly in patients with conduction abnormalities or impaired ventricular function (see Prescribing Information)

---

## Benefits of 'Tenormin'

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### in angina

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## Stable and unstable angina

'Tenormin' is a recommended first-line treatment of stable

## Long-term treatment

The clinical value of 'Tenormin' is well established in

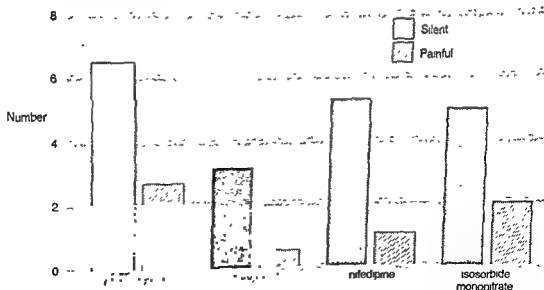
patients showed that 'Tenormin' was significantly

## Coadministration of calcium antagonists and 'Tenormin' in unstable angina

'Tenormin' + nifedipine

'Tenormin' + nifedipine

**Figure 9.**  
Comparative anti-anginal efficacy of 'Tenormin', nifedipine and ISMN  
(silent and painful episodes)



## Cardioprotective effect of beta-blockers in angina

be an important advantage in an anti-anginal drug

Weissberg<sup>81</sup> has postulated how beta-blockers may break the link between ischaemia and irreversible

the reduction of infarct size and incidence of arrhythmias<sup>58</sup>

A study reported in 1986 has provided additional evidence in support of a cardioprotective effect of beta-blockade in patients with more serious unstable

their combination on the incidence of recurrent ischaemia or MI within 48 hours of treatment.

Metoprolol alone and metoprolol with nifedipine were the only treatments which resulted in a significantly lower incidence of 44% over metoprolol alone.

protecting against further ischaemia.<sup>82</sup>

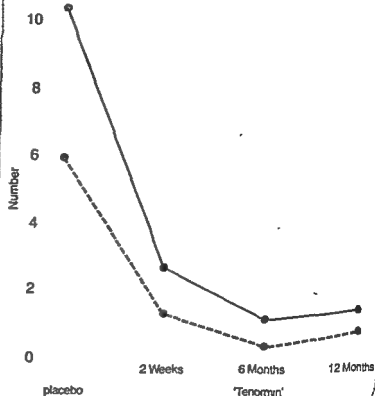
Nifedipine administered alone resulted in a trend towards a more or less significant reduction in the incidence of further ischaemia.

**Simple once-daily dosage** The optimum dose and frequency have been investigated in a number of blind cross-over studies

Studies have generally shown that 'Tenormin' gives effective control of angina throughout 24 hours, and that twice-daily dosing gives no further advantage over once-daily dosing in almost all patients<sup>19,21,28,32,40,41,44,50,54,57</sup> Some physicians have concluded that, "the 24-hour beta-blocking effect of ['Tenormin'] might be



Figure 10. Effect of Tenomin on the number of falls in the elderly.



Following the study, the number of falls in the placebo group was significantly higher than in the Tenomin group.

#### Conclusion

The study concluded that the use of Tenomin significantly reduced the number of falls in the elderly.

improvement was not the result of any formal exercise training effect <sup>48</sup>

Schneider concluded that the use of Tenomin significantly reduced the number of falls in the elderly.

## Cardioprotective effect of beta-blockers in angina

be an important advantage in an anti-anginal drug

Weissberg<sup>81</sup> has postulated how beta-blockers may break the link between ischaemia and irreversible

arrhythmias<sup>58</sup>

A study reported in 1986 has provided additional evidence in support of a cardioprotective effect of beta-blockade in patients with more serious unstable angina<sup>82</sup> This double-blind, placebo-controlled, randomised, multicentre study was designed to determine the effect of metoprolol, nifedipine and their combination on the incidence of recurrent ischaemia or MI within 48 hours of treatment.

Metoprolol alone and metoprolol with nifedipine were the only treatments which resulted in a

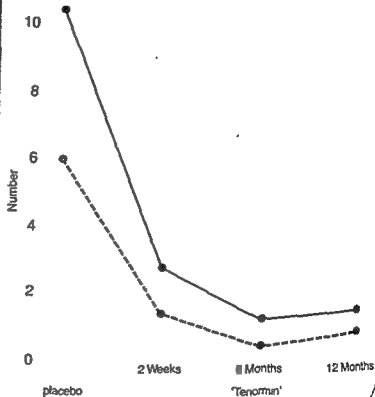
Nifedipine administered alone resulted in a trend towards a worse outcome such that the study was stopped prematurely, " *it was felt unethical to continue nifedipine monotherapy trial medication* "<sup>82</sup>

## Simple once-daily dosage

The optimum dose and frequency have been investigated in a number of blind cross-over studies

Some physicians have concluded that, " *... the 24-hour beta-blocking effect of [Tenormin] might be*

**Figure 10.** Frequency of angina (●—●) and glyceryl trinitrate consumption (●—●) during placebo and early and long-term 'Tenormin' treatment



Following the initial observed decrease in the attack rate (1%),

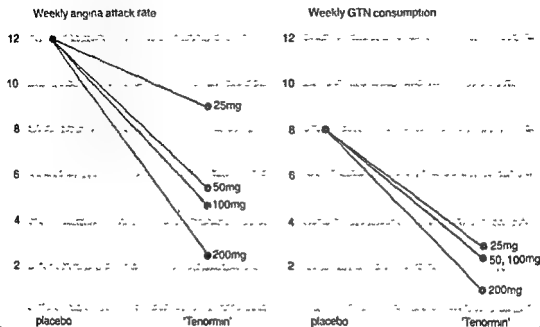
months.<sup>48</sup>

During the next nine months, the anti-anginal effect, as represented by these measures, remained constant and there was no increase in serum drug concentration or

training effect.<sup>49</sup>

Schwartz concluded that, "The beneficial effects of

**Figure 12. Effect of different doses of 'Tenormin' on angina in 10 patients**



## Summary: 'Tenormin' in angina

- Effective prophylaxis in classical angina of effort
- Effective in unstable angina occurring at rest and on effort
- Reduces heart rate when taken at 24 hours pre-exercise
- Overall, more effective than nifedipine as monotherapy
- Addition of calcium antagonists can provide extra benefit in severe or unstable angina
- Cardioprotective beta-blockade benefits the patient at risk from MI or sudden death
- Proven long-term efficacy
- Simple once-daily dose for most patients
- Low level of side-effects

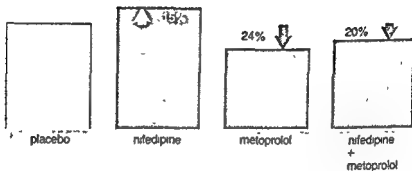
**Figure 11.**  
Myocardial infarction or recurrent ischaemia  
within 48 hours

100

(No prior  $\beta$ -blockade n=338)



50



other

**100mg/day – optimal in most cases**

Most investigators agree that the optimum dose is 1-2 mg/kg/day.

- 23 ROY P, DAY L and SOWTON L  
Effect of new beta-adrenergic blocking agent, atenolol ('Tenormin'), on pain frequency, trinitrin consumption and exercise ability  
*Br Med J* 1975, 3: 195-97
- 24 ROY P, DAY L and SOWTON L  
Effect of new beta-adrenergic blocking agent, atenolol ('Tenormin'), on pain frequency, trinitrin consumption and exercise ability  
*Br Med J* 1975, 3: 195-97
- 25 ROY P, DAY L and SOWTON L  
Effect of new beta-adrenergic blocking agent, atenolol ('Tenormin'), on pain frequency, trinitrin consumption and exercise ability  
*Br Med J* 1975, 3: 195-97
- 26 ROY P, DAY L and SOWTON L  
Effect of new beta-adrenergic blocking agent, atenolol ('Tenormin'), on pain frequency, trinitrin consumption and exercise ability  
*Br Med J* 1975, 3: 195-97
- 27 FANANAPAZIR L and BRAY C  
Comparison of oxyfedrine and atenolol in angina pectoris - a double-blind study  
*Br J Clin Pharmacol* 1985, 20: 405-10
- 28 MAJID PA, VAN DER VEGH WJF, DE FEJTER PJ, WARDEH R, VAN DER WALL EE and ROOS JP  
Once daily atenolol ('Tenormin') in the treatment of angina pectoris. Observations on clinical efficacy, pharmacokinetics and pharmacodynamics  
*Eur J Cardiol* 1979, 9 (6): 419-35
- 29 RADICE M, ANTONGIOVANNI GB,  
Effect of atenolol on the clinical and hemodynamic response to exercise in patients with angina pectoris  
*Int J Clin Pharmacol Res* 1982, 11 (2): 119-26
- 30 QUYYUMI AA, WRIGHT C, MOCKUS L and FOX KM  
Effect of partial agonist activity in  $\beta$  blockers in severe angina pectoris - a double-blind comparison of pindolol and atenolol  
*Br Med J* 1984, 289: 951-53
- 31 FINDLAY IN, DARGIE HJ, GILLEN G and ELLIOTT AT  
The treatment of angina pectoris with calcium channel and beta-blockers, efficacy and effect on cardiac function  
*J Am Coll Cardiol* 1984, 3 (2 Pt 2): 482
- 32 BOYLE RM, BRAY CL, NAQVI N, CROXSON RS and CRUICKSHANK JM  
A comparison of once and twice daily atenolol for angina pectoris  
*Int J Cardiol* 1983, 3: 25-35
- 33 WHEATLEY D  
A comparison of diltiazem and atenolol in angina.  
*Postgrad Med J* 1985, 61: 785-89
- 34 KOHLI RS, KHURMI NS, KARDASH MM, HUGHES LO, LAHIRI A and RAFTERY EB  
Double-blind randomized comparative evaluation of bisoprolol and atenolol in angina pectoris  
Cardiovascular Pharmacotherapy International Symposium, Apr 22-25th, 1985, Geneva Abstract 33
- 35 FINDLAY IN, GILLEN G, ELLIOTT AT and DARGIE HJ  
The treatment of angina pectoris with calcium channel and beta-blockers, efficacy and effect on cardiac function  
*J Am Coll Cardiol* 1984, 3 (2 Pt 2): 482
- 36 WESTERMANN KW and LANGBEHN AF  
Clinical and hemodynamic reactions of coronary patients before and after beta-blockade with atenolol  
Eighth World Congress of Cardiology, Sept 17-23rd, 1978, Tokyo Abstract 380, 182
- 37 SANCHEZ CASCO S A, GAUSI GENE C, RICHART MARTINEZ JA, DE RABAGO GONZALEZ P, BROS CAIMARI R and GARCIA CALLEGO F  
Ensayo clinico del nuevo betabloqueante atenolol  
*Rev Esp Cardiol* 1977, 30 (5): 545-48
- 38 FINDLAY IN and DARGIE HJ  
The effects of nifedipine, atenolol and that combination on left ventricular function  
*Postgrad Med J* 1983, 59 (Suppl 2): 70-73
- 39 FINDLAY IN, McLEOD K, FORD M, GILLEN G, ELLIOTT AT and DARGIE HJ  
Treatment of angina pectoris with nifedipine and atenolol. Efficacy and effect on cardiac function  
*Br Heart J* 1986, 55: 240-45
- 40 MÄKYNEN P and RUOSTEENOJA R  
Atenolol once-daily in angina  
Eighth World Congress of Cardiology Sept 17-23rd 1978, Tokyo Abstract 382, 183
- 41 BACHMANN M, RAEBER E, BURCKHARDT D et al  
Atenolol in der behandlung der angina pectoris  
*Schweiz Med Wochenschr* 1979, 109 (47): 1857-60
- 42 GRUPPILLO P, BATTAGLIA R, MASONI C and MASONI A  
Therapeutic comparison between atenolol and nifedipine in effort angina  
*Drugs* 1983, 25 (Suppl 2): 194-95

# References

- 1 KANNEL WB and FEINLEIB M  
Natural history of angina pectoris in the  
Framingham study Prognosis and survival  
*Am J Cardiol* 1972, 29 154-63
- 2 FRANK CW, WEINBLATT E and SHAPIRO S  
Angina pectoris in men Prognostic significance  
of selected medical factors  
*Circulation* 1973, 47 509-17
- 3 BLOCK WJ, CRUMPACKER EL, DRY TJ *et al*  
Prognosis of angina pectoris Observations in  
6882 cases  
*JAMA* 1952, 150 259-64
- 4 MILLER AB  
Mixed ischemic subsets Comparison of the  
mechanisms of silent ischemia and mixed angina  
*Am J Med* 1985, 79 (Suppl 3A) 25-29
- 5  
Transient ischemia in angina pectoris frequent  
silent events with everyday activities  
*Am J Cardiol* 1985, 56 34E-38E
- 6 COHN PF  
Silent myocardial ischaemia classification,  
prevalence, and prognosis  
*Am J Med* 1985, 79 (Suppl 3A) 2-6
- 7 ERIKSEN J and THAULOW E  
Follow-up of patients with asymptomatic  
myocardial ischaemia  
In Rutishauser W and Roskamm H, eds *Silent  
myocardial ischaemia*  
Berlin Springer Verlag, 1984, 156-64
- 8 LANGOU RA, HUANG EK, KELLEY MJ and  
COHEN LS  
Predictive accuracy of coronary artery  
calcification and abnormal exercise test for  
coronary artery disease in asymptomatic men  
*Circulation* 1980, 62 1196-1203
- 9 HICKMAN JR, UHL GS, COOK RL, ENGEL PJ  
and HOPKIRK A  
A natural history study of asymptomatic coronary  
disease  
*Am J Cardiol* 1980, 45 422
- 10 TEMKIN LP  
Tailoring combination therapy for angina  
patients  
*PA Drug Update* 1984, 4 (7) 27-36
- 11 HOOD WP  
Medical management of ischemic heart disease  
*Ala J Med Sci* 1985, 22 (3) 266-70
- 12 WILNER GN  
Coronary artery disease Natural history  
*Cardiovasc Rev Rep* 1985, 6 (6) 808-13
- 13 BRAUNWALD H and COHN PF  
Unstable angina pectoris
- 14 JULIAN DG
- 15 STEPHAN K, ABENDROTH RR, HUBNER H  
and MEESMANN W  
Effects of the new beta-adrenergic agent atenolol  
Seventh European Congress of Cardiology,  
Abstract Book II 1976, 99
- 16 SIMONSEN S  
Effect of atenolol (ICI 66082) on coronary  
haemodynamics in man  
*Br Heart J* 1977, 39 1210-16
- 17 ASTROM H and VALLIN H  
Effect of a new beta-adrenergic blocking agent,  
ICI 66082, on exercise haemodynamics and  
airway resistance in angina pectoris  
*Br Heart J* 1974, 36 1194-1200
- 18 REUBEN SR, BLAKE P and WHITAKER EV  
The effect of atenolol on exercise performance in  
angina pectoris.  
Eighth World Congress of Cardiology, Sept 17-  
23rd, 1978, Tokyo Abstract 403, 188
- 19 NOER GH and EKELI T  
Atenolol once daily in angina pectoris  
*Curr Ther Res* 1978, 24 (1) 17-25
- atenolol  
*Br Heart J* 1978, 40 998-1004

- 64 FINDLAY I, GILLEN G, ELLIOTT AT and DARGIE HJ  
Calcium antagonists and beta-blockers in angina  
A beneficial drug interaction?  
*Eur Heart J* 1985, 6 (Suppl 1) 80
- 65 DeBUTLEIR M, ROWLAND E and  
propranolol or atenolol  
*Br J Clin Pharmacol* 1985, 20 (3) 251p
- 67 BERTHOUD P, BASSAND J, SCHIPMAN C  
*et al*  
Comparative anti-ischaemic activity of atenolol  
and diltiazem. A randomized, single-blind, cross-  
over study using computerized exercise tests  
*Rev Med Int* 1985, 6 259-65
- 68 LESSEM J  
Combined therapy with Ca-antagonists and beta-  
adrenergic receptor blocking agents in chronic  
stable angina  
*Acta Med Scand* 1984, 215 (Suppl 681) 83-90
- 69 LOGAN R, IKRAM H, WEBSTER MW and  
GUPPY W  
Comparison of nifedipine hydrochloride and  
atenolol in stable angina pectoris  
*NZ Med J* 1985, 98 (789) 912
- 70 HULTGREN HN, PFEIFFER JE, ANGEL WW  
and BILISOLY J  
Unstable angina: comparison of medical and  
surgical management.  
*Am J Cardiol* 1977, 39 734-40
- 71 WILES WJ, PEDUZZI PN and HAMMOND G  
Preoperative predictors of operative mortality for  
coronary by-pass in patients with unstable angina  
pectoris  
*Am J Cardiol* 1977, 39 939-43
- 72 MULLER JE, TURI ZG, PEARLE DL *et al*  
Nifedipine and conventional therapy for unstable  
angina pectoris: a randomized, double-blind  
comparison  
*Circulation* 1984, 69 728-39
74. HUGENHOLTZ PG, MICHELS HR, SERRUYS  
*Am J Cardiol* 1981, 47 163-73
- 75 GUAZZI M, FIORENTINI C, POLESE A,  
MAGRINI F and OLIVARI MT  
Treatment of spontaneous angina pectoris with  
beta-blocking agents. A clinical,  
electrocardiographic, and haemodynamic  
appraisal  
*Br Heart J* 1975, 37 1235-45
- 76 GERSTENBLITH G, OUYANG P, ACHUFF SC  
*et al*  
Nifedipine in unstable angina. A double-blind  
randomized trial  
*N Engl J Med* 1982, 306 885-94
- 77 VEDIN A and WILHELMSSON C  
Medical treatment of ischaemic heart disease -  
beta-blockers  
*Eur Heart J* 1985, 6 (Suppl A) 13-27
- 78 FISHER ML  
Beta-blockers in unstable angina  
In: Plotnick GD, ed. Unstable angina. A clinical  
approach  
New York: Futura, 1985, 213-43
- 79 ROBERTSON RM, WOOD AJJ, VAUGHN WK  
and ROBERTSON D  
Exacerbation of vasotonic angina pectoris by  
propranolol  
*Circulation* 1982, 65 281-85
- 80 GODENIR JP, AMOR M, CHERRIER F
- 81 WEISSBERG PL  
Treatment of angina  
*J Clin Hosp Pharm* 1982, 7 145-53
- 82 LUBSEN J

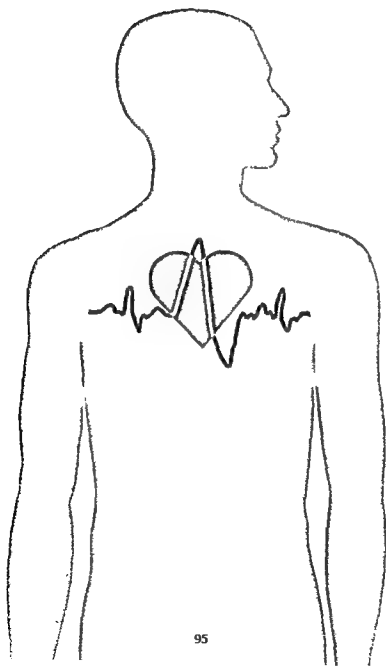


- 43 BACKMAN H, NURMI H and SAKO S  
Atenolol in angina pectoris - preliminary results  
of an ergometric dose-finding study  
*Acta Ther* 1978, 4 (3) 267-74
- 44 JACKSON G, SCHWARTZ J, KATES RE,  
WINCHESTER M and HARRISON DC  
Atenolol Once-daily cardioselective beta-blockade for angina pectoris  
*Circulation* 1980, 61 (3) 555-60
- 45 TAIANO A, ARIAS ID CAS,  
LAMPRO... ..
- 46 ZAKI MASUD AR, DEAN DC and NAUGHTON J  
Improved exercise performance following single daily dose of atenolol in stable angina  
*Int J Cardiol* 1983, 3 15-24
- 47 MAGNANI II BR,... AM  
Cardiovascular antagonism between atenolol and ...  
*Drugs* 1983, 25 (Suppl 2) 166-71
- 48 SCHWARTZ JB  
Atenolol in the treatment of angina Once daily cardioselective beta-blockade for angina pectoris  
*Drugs* 1983, 25 (Suppl 2) 160-65
- 49 SRIVANASONT N, SAHASAKULY, CHAITHIRAPHAN S and CHAROENCHOB N  
Efficacy of atenolol, a cardioselective beta-adrenoceptor antagonist in angina pectoris  
*Fifth Asian Congress of Cardiology*, Nov 25-29th, 1984, Bangkok, 215A-16A
- 50 HAGHELT T, PINBORG T and THAYSEN P  
Atenolol ('Tenormin') i behandlingen af angina pectoris  
*Ugeskr Laeger* 1980, 142 (38) 2475-78
- 51 MATHUR VS  
Efficacy of a new cardioselective long acting beta blocker in stable angina pectoris comparison of once daily atenolol with propranolol  
*Circulation* 1983, 66 (4 Part 2) Abstract 85
- 52 THOMPSON R  
Influence of pindolol and atenolol on left ventricular function during exercise in patients with stable angina pectoris  
*Cardiovascular Pharmacotherapy International Symposium*, Apr 22-25th, 1985, Geneva  
Abstract 22
- 53 FLORAS JS, JONES JV, HASSAN MO and SLEIGHT P  
Ambulatory blood pressure during once-daily randomised double-blind administration of atenolol, metoprolol, pindolol and slow-release propranolol  
*Br Med J* 1982, 285 1387-92
- 54 HARRY I JACQUE... ..  
... .. of Cardiology, Sept 17-21st, 1978, Tokyo Abstract 400 187
- 55 BISCHOFFK.  
Wirkung von atenolol auf die Beschwerdesymptomatik Koronarkranker  
*Munch Med Wochenschr* 1981, 123 (56) 1337-40
- 56 De DIVITIIS O De... .. NA  
... ..  
*Clinical Cardiol* 1981; 11 2088-96
- 57 SHAPIRO W  
Comparison of once-daily atenolol and placebo in the treatment of stable angina pectoris  
*Cardiovasc Rev Rep* 1985, 6 (12) 1292-1304
- 58 YUSUF S, PETO R, LEWIS J, COLLINS R and SLEIGHT P  
Beta-blockade during and after myocardial infarction An overview of the randomized trials  
*Prog Cardiovasc Dis* 1983, 27 (5) 335-71
- 59 KJEKSJUS J  
Comments - beta-blockers Heart rate reduction a mechanism of benefit  
*Eur Heart J* 1983, 6 (Suppl A) 29-30
- 60 GLAZIER JJ, CHERCHIA S, SMITH GC et al  
Beta-blockers for angina pectoris How do they really work?  
*Clin Sci* 1986, 70 (Suppl 13) 1-7
- 61 ... ..  
... .. calcium antagonist, administered in patients with exertional and rest angina  
*Br Heart J* 1985, 54 (6) 643-44 and publication in press
- 62 FOX KM, DEANFIELD J, KRICKLER S, RIBEIRO P and WRIGHT C  
The influence of cigarette smoking on the medical management of angina  
*Drugs* 1983, 25 (Suppl 2) 177-80

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**'Tenormin'**  
**in the treatment**  
**of arrhythmias**

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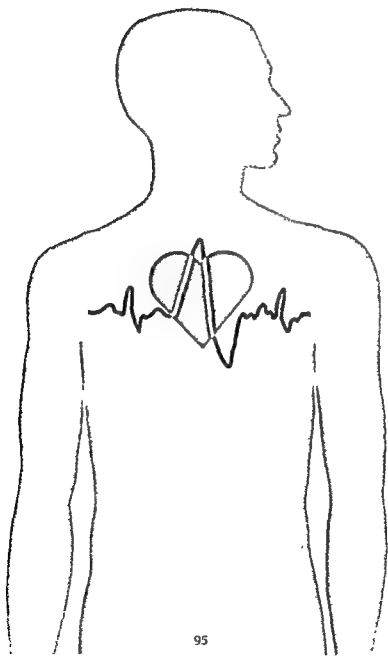




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**'Tenormin'**  
in the treatment  
of arrhythmias

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## Anti-arrhythmic effects of beta-blockade

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Beta-blockers are effective anti-arrhythmic agents eg when excessive sympathetic stimulation results in sinus tachycardia and ectopic pacemaker activity  
Beta-blockade overcomes this by:

- ☐ depressing excitability and automaticity
- ☐ slowing heart rate
- ☐ prolonging refractory period
- ☐ depressing conductivity
- ☐ preventing ischaemia

The importance of more controversial properties of beta-blockers, such as membrane stabilising activity (MSA), is unclear. For instance, practolol, with no MSA, has proven anti-arrhythmic action whereas dextropropranolol, which has MSA properties, has no anti-arrhythmic action.<sup>1</sup>

In the opinion of Scheidt, "Beta-blockers are . . .

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## Consistent electrophysiological properties of 'Tenormin'

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The importance of consistent electrophysiological properties of beta-blockers has been emphasised by the results of a study by Scheidt et al.<sup>2</sup> This study compared the effects of tenormin (acebutolol) with those of propranolol on the electrophysiological properties of the heart. The results showed that tenormin had a more consistent effect on the heart than propranolol, particularly in terms of its effect on the heart rate and the refractory period of the ventricle.

reduction in heart rate), sinus node recovery time,

refractory period of the ventricle.<sup>3,4</sup>

In contrast to other commonly used beta-blockers, 'Tenormin' has been shown to have a wider range of favourable electrophysiological properties<sup>3</sup> (Figure 1)

**Figure 1. Electrophysiological properties of  $\beta$ -blockers (investigations in man)**

	'Tenormin'	metoprolol	propranolol	pindolol	oxprenolol	acebutolol
Sinus cycle length	○	○	○	○	○	■
Sinus node recovery time	○	ns	nr	ns	ns	ns
SA conduction time	○	○	nr	ns	○	nr
Atrium effective refractory period (ERP)	○	ns	○	■	ns	ns
Atrium functional refractory period (FRP)	○	ns	nr	○	ns	nr
AV node ERP	○	nr	○	nr	nr	nr
AV node FRP	■	○	○	○	■	○
AV node conduction time	○	○	○	○	○	○

○ = significantly prolonged; ns = not significant; nr = not reported

Di-Biase and co-workers concluded that, "Tenormin" possesses electrophysiologic properties similar to those of most previously studied beta-blocking agents except for a more pronounced action on sinus node

**AV node re-entrant supraventricular tachycardias."**

Furthermore, "... the lack of adverse effects on infra-His conduction allows its use also in subjects with intraventricular conduction disturbances."<sup>4</sup> However, caution may be necessary in patients with sinus dysfunction (see also Prescribing Information)

## Therapeutically-desirable effect on supraventricular arrhythmias

### Pacing-induced arrhythmias

tachycardias in 68% of patients by normalising  
ventricular rate<sup>6</sup>

significance of the results still require to be evaluated

### Supraventricular arrhythmias

Four studies described the successful use of intravenous  
or oral 'Tenormin' in patients with supraventricular  
arrhythmias such as paroxysmal supraventricular

atrial flutter or atrial fibrillation responded partially or  
fully to 'Tenormin' whilst 33% of patients with

Additional benefit derived from 'Tenormin' treatment  
included stabilisation or favourable reduction in blood  
pressure, resolution of symptoms of heart failure  
secondary to arrhythmias<sup>10</sup> and a significant fall in heart  
rate<sup>9</sup>

\*As defined by the investigator



---

## Many arrhythmias controlled by standard 'Tenormin' doses

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### Dose regime and onset of action

Effective doses of 'Tenormin' varied between studies, for instance 0.1 mg/min.<sup>10</sup> 50-150mg/day.<sup>9</sup>

Following intravenous administration of 'Tenormin', the anti-arrhythmic action was observed after two minutes, stabilised after 5-10 minutes and remained constant for a minimum of two hours.<sup>10</sup> On the other hand, the effect of oral treatment developed more gradually over 24 hours.<sup>10</sup>

Most patients' arrhythmias were satisfactorily controlled on standard 'Tenormin' dose regimes although occasionally the higher doses were required with or without concomitant lignocaine therapy.<sup>7</sup>

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## A well-tolerated treatment for ventricular arrhythmias

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Ventricular arrhythmias require careful treatment mainly

infarction.<sup>2</sup>

Several clinical studies have been conducted in which 'Tenormin' was administered intravenously and/or orally.

ventricular flutter.<sup>7,10-14</sup>

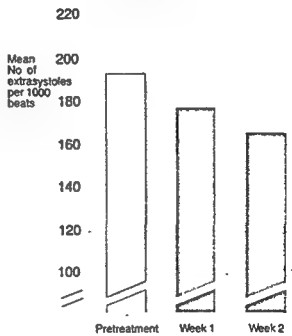
### Extrasystoles

In three studies, oral and intravenous administration of 'Tenormin' resulted in a complete or partial response

patients.<sup>11</sup>

...the fact that the incidence of ventricular extrasystoles is high in the post-infarction period, the use of beta-blockers is recommended. The effect of Tenormin on ventricular extrasystoles is shown in Figure 2.

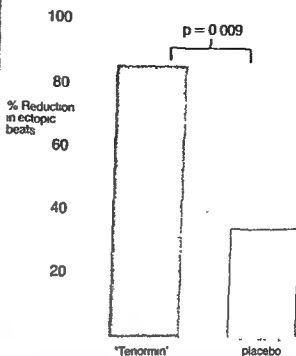
**Figure 2. Effect of 'Tenormin' on ventricular extrasystoles**



## Ectopic beats

Ventricular ectopic beats are presented in approximately 80% of post-infarction patients and indicate an increased risk of cardiac mortality.<sup>14</sup> It is thought that beta-blockers may reduce the incidence of sudden death by preventing ventricular fibrillation and ectopic beats.<sup>14</sup>

**Figure 3. Effect of 'Tenormin' on ventricular ectopic beats**



This was further confirmed by the same clinicians in a randomised comparison of 'Tenormin' with prajmalium bitartrate in which 'Tenormin' and prajmalium reduced ventricular ectopic beats by 91% and 77% respectively.

## Other ventricular arrhythmias

Other arrhythmias which 'Tenormin' has been shown to control include paroxysmal ventricular tachycardia and ventricular flutter (100% of cases reported),<sup>7</sup> ventricular couplets (71%)<sup>11</sup> and ventricular tachycardia (40%)<sup>11</sup>

---

## Arrhythmias associated with myocardial infarction

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### Rationale for beta-blockers

It is well accepted that certain beta-blockers are effective

death

It has been postulated that immediate treatment with an anti-arrhythmic agent, such as a beta-blocker, should be instituted. Several non-randomised studies have shown

Trial (BHAT), there was a significant decrease in the number of premature ventricular beats<sup>20</sup> and a small but non-significant decrease in ventricular ectopic activity<sup>21</sup> after oral beta-blockade compared with placebo

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## Combined intravenous and oral 'Tenormin' for effective control of post-infarction arrhythmias

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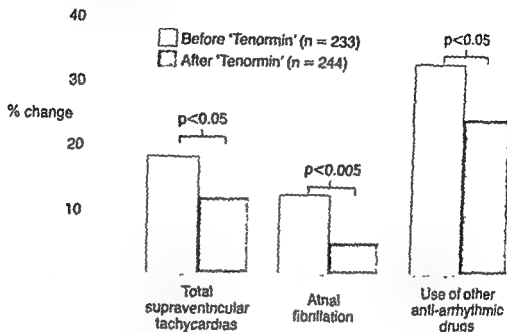
### Supraventricular arrhythmias

Yusuf and co-workers conducted a randomised study in 477 post-infarction patients who presented within 12

discharged

'Tenormin' significantly reduced the frequency of

Figure 4. Effect of 'Tenormin' on post-infarction supraventricular arrhythmias



## Ventricular arrhythmias

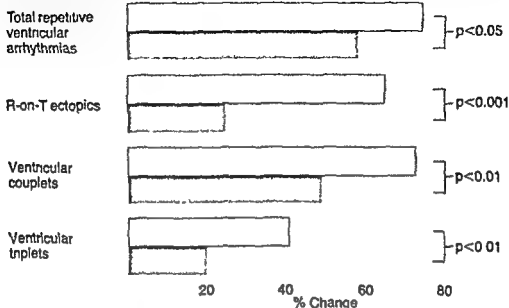
In the same study described above, Yusuf *et al* monitored ventricular arrhythmias using 24-hour

'Tenormin' provided effective control of the majority of the observed arrhythmias (Figure 5), with equivocal results on ventricular tachycardias.<sup>15,22</sup> For example, 'Tenormin' induced a fall in mean heart rate, reduced the mean (24 hour total) number of ventricular ectopic beats ( $p < 0.001$ ); reduced the incidence of R-on-T ventricular ectopic beats ( $p < 0.001$ ), reduced the incidence of

'Tenormin' (n=5)

**Figure 5. Effect of 'Tenormin' on post-infarction ventricular arrhythmias (24h recordings; n = 182)**

□ Before 'Tenormin'  
 ■ After 'Tenormin'



**Summary:  
 'Tenormin' in the  
 treatment of  
 arrhythmias**

- Effective in a wide range of arrhythmias
- Unlike many other beta-blockers including other cardioselective agents, 'Tenormin' prolongs atrial refractoriness
- Well tolerated by a wide variety of patients including those with life-threatening arrhythmias

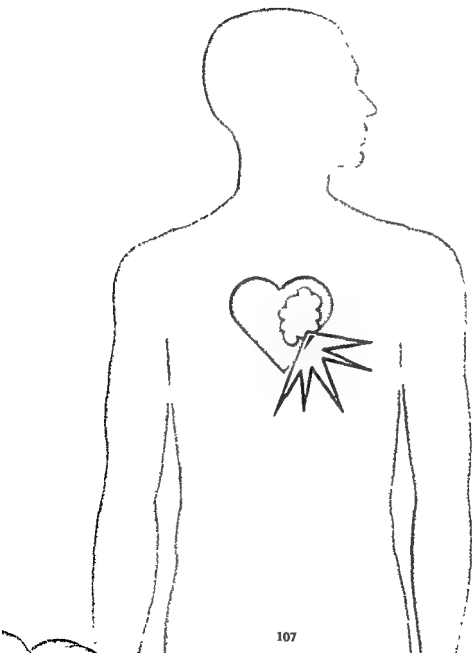
# References

- 1 JEWITT DE and SINGH BN.  
The role of beta-adrenergic blockade in myocardial infarction  
*Prog Cardiovasc Dis* 1974, 16: 421-38
- 2 SCHEIDT S  
Beta-blockade for angina and arrhythmias  
Present status  
*Drugs* 1983, 25 (Suppl 2) 153-59
- 3 ROBINSON C, BIRKHEAD J, CROOK B, JENNINGS K and JEWITT D  
Clinical electrophysiological effects of atenolol - a new cardioselective beta-blocking agent  
*Br Heart J* 1978, 40: 14-21
- 4 DI BIASE M, FAVALE S and RIZZON P  
Electrophysiologic properties of intravenous 'Tenormin' in man  
*Eur J Cardiol* 1979, 9 (4) 333-42
- 5 Data on file at ICI
- 6 HOMBACH V, HOPP HW, BRAUN V *et al*  
Relevance of physical activity to the anti-arrhythmic effects of beta-blockade on supraventricular tachycardias  
*Drugs* 1983, 25 (Suppl 2) 186-92
- 7 SCHLEY G, BECKMAN R and HENGSTEBECK W  
The treatment of acute cardiac dysrhythmias with atenolol ('Tenormin') particularly after myocardial infarction  
*Z Kardiol* 1978, 67: 280-88
- 8 WINCHESTER MA, JACKSON G, MELTZER RS *et al*  
Intravenous atenolol and acebutolol in the treatment of supraventricular arrhythmias  
*Circulation* 1978, 58 (4) 11-49
- 9  
fibrillation  
*Boll Soc Ital Cardiol* 1978, 23: 1591-96
- 10 SIRBULESCU R  
Atenolol in the treatment of cardiac dysrhythmia  
*Acta Ther* 1977, 3 109-116
- 11
- 12
- 13
- 14 KORST HA, BRANDES JW, PEDERSON SU and LITTMANN KP  
Atenolol and ventricular ectopic beats  
*Drugs* 1983, 25 (Suppl 2), 196-97
- 15 ROSSI PR, YUSUF S, RAMSDALE D, FURZEL and SLEIGHT P  
Reduction of ventricular arrhythmias by early intravenous atenolol in suspected acute myocardial infarction  
*Br Med J* 1983, 286: 306-10
- 16 JEWITT DE, MERCER CJ and SHILLINGFORD JP  
Practolol in the treatment of cardiac dysrhythmias due to acute myocardial infarction  
*Lancet* 1969, 2: 227-30
- 17 SANDLER G and PISTEVOS AC  
Use of oxprenolol in cardiac arrhythmias associated with acute myocardial ischaemia  
*Br Med J* 1971, 1: 254-57
- 18 LEMBERG L, ARCEBAL AG, CASTELLANOS A and SLAVIN D  
Use of alprenolol in acute cardiac arrhythmias  
*Am J Cardiol* 1972, 30: 77-81
- 19
- 20 LICHSTEIN E, MORGANROTH J, HARRIST R
- 21 DE SOYZA N, MURPHY ML, TERRY L and THOMPSON C  
The effect of propranolol on the course of
- 22 YUSUF S, ROSSI P, RAMSDALE D *et al*

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## **'Tenormin' in acute myocardial infarction**

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### myocardial

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In treating patients who have coronary artery disease and who display signs of ischaemia, a major aim is to

'Tenormin' can prevent pre-infarct angina developing into an acute MI <sup>2</sup>

If a patient suffers an MI, short-term treatment with intravenous and oral 'Tenormin' early in the evolution of the infarct can reduce the extent of the infarction and save lives <sup>3</sup>

Those who survive an acute infarction are known to be at increased risk of dying suddenly or developing further

## Why use a beta-blocker?

An infarction may arise from over-activation of the sympathetic nervous system which increases cardiac workload beyond the capacity of atheromatous coronary

sympathetic activity by a number of different

## **'Tenormin' treatment and the progression of pre-infarct angina to full infarction**

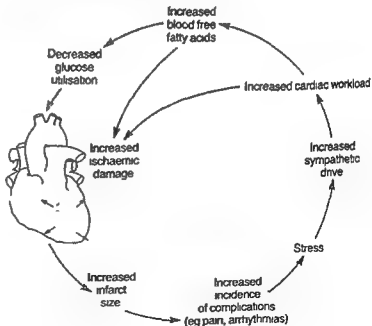
### **Characteristics of pre-infarct angina**

Pre-infarct angina – also known as crescendo, accelerated or progressive angina or threatened MI – may occur during exercise or at rest and may be easily

It is characterised by severe pain lasting several hours and severe S-T segment elevation or depression. Depending on the severity, there may also be a low level of cardiac-enzyme release into the circulation – an indication that a frank infarction is impending.

**Figure 1.**

Representation of the possible vicious cycle involving metabolic consequences of sympathetic stimulation in connection with a myocardial infarction



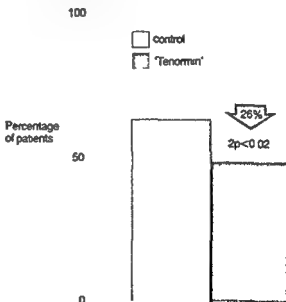
Adapted from Opie LH, et al *Lancet* 1977, 2: 890-92

## Risks to the patient

'Tenormin'  
reduces the risk of  
developing  
full MI

An estimated 45% of patients with acute MI have prodromal symptoms (eg chest pain) <sup>1</sup> In one series of 235 patients with prodromal symptoms, early treatment during the warning period may prevent progression to irreversible cardiac damage and save lives

Figure 2.  
Reduced progression from threatened to acute MI



mortality.<sup>2</sup> There was no indication that 'Tenormin' caused any irreversible effect on cardiac function.<sup>2</sup> The results of this encouraging trial provided the basis for a large-scale study<sup>3</sup> designed to protect high-risk patients

In a further study, patients at special risk of developing a full MI were treated with 'Tenormin' for 2 weeks before surgery. This treatment was found to be effective in protecting against progression of their pre-infarct angina to full infarction.<sup>39</sup> (Figure 3)

Thus, patients at special risk may be afforded protection from a full MI by early short-term administration of 'Tenormin'

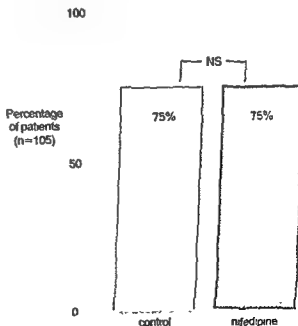
A controlled study examined the outcome of 105

patients with pre-infarct angina, who were treated with 'Tenormin' for 2 weeks before surgery, to protect against progression of their pre-infarct angina to full infarction.<sup>39</sup> (Figure 3)

## Calcium antagonists in patients with deteriorating pre- infarct angina

**Figure 3.**

No effect on progression of threatened to acute MI



sympathetic activity (with a consequent increase in heart

---

## **'Tenormin' in acute MI**

---

### **Characteristics of myocardial infarction**

Myocardial infarction usually occurs after several hours of pain and its severity depends on the degree of imbalance between oxygen supply and demand

interruption of the oxygen supply

### **Risks to the patient**

## 'Tenormin' saves lives

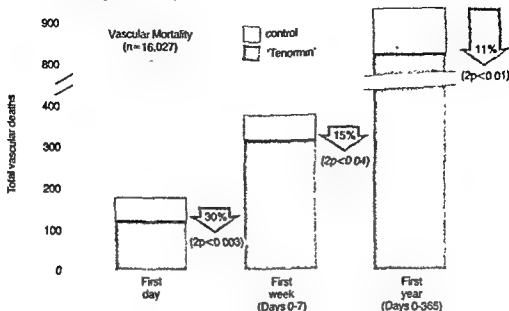
The International Study of Infarct Survival (ISIS), reported in 1986, demonstrated that short-term

centres in 11 countries.

The patients were a low-risk group (individuals with hypotension or significant bradycardia were excluded)

Beta-blockade was maintained with oral 'Tenormin' (100 mg/day) for a further seven days.<sup>3</sup>

**Figure 4.**  
The effect of early intervention with 'Tenormin' in reducing mortality in acute myocardial infarction



## The benefits of 'Tenormin' in acute MI

### 'Tenormin' reduces infarct size

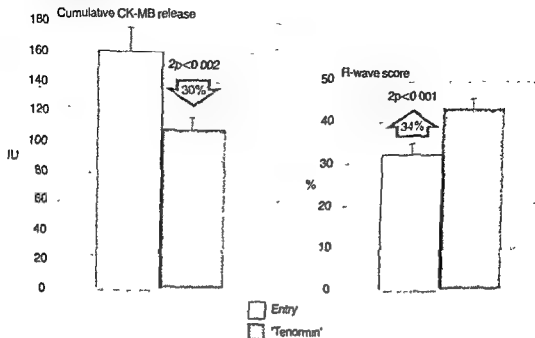
The results of ISIS suggested that early 'Tenormin' treatment

mechanism by which short-term administration of intravenous 'Tenormin' protected against mortality was elucidated by the ISIS pilot trial<sup>2</sup> (see also earlier in this chapter).

The extent of myocardial damage was measured by cardiac-enzyme (creatinine kinase isoenzyme - CK-MB) release and R-wave score on the ECG.<sup>2</sup> Both tests produced indirect measurements which, together, correlated well with infarct size.<sup>3</sup> Short-term intravenous and oral administration of 'Tenormin' in a group of 1700



**Figure 5.**  
Cumulative CK-MB release and R-wave scores in patients with initial definite MI



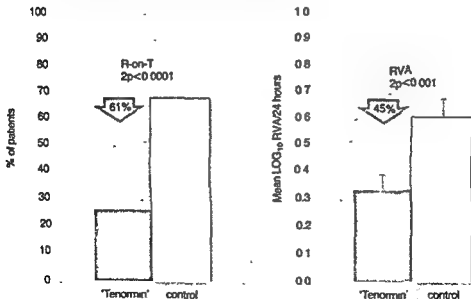
## Anti-arrhythmic action

reduced after beta-blockade

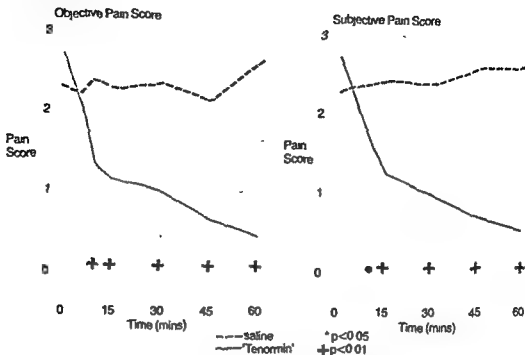
Anti-arrhythmic action during MI dependence on

monitored for ventricular premature complexes by 24-

**Figure 6.**  
Reduction in R-on-T ectopic complexes and repetitive  
ventricular arrhythmias (RVA) in the first 24 hours



**Figure 7.**  
Reduced chest pain after 'Tenormin'



## 'Tenormin' relieves chest pain

Pain during infarction is probably related to ischaemia in the necrotic area which stimulates sensory neurones (Figure 1). The pain triggers a further release of catecholamines and beta-blockers such as 'Tenormin', which relieve pain, also decrease heart rate, blood pressure and ECG abnormalities<sup>11,15,15</sup>

Our group demonstrated that the reduction in cardiac

[illegible]

that, "Beta-blockers must be given a more important place in the management of chest pain due to myocardial infarction"<sup>63</sup>

## Calcium antagonists and ACE inhibitors in MI

A small number of other trials, including a large, multicentre, placebo-controlled trial, have also demonstrated a reduction in chest pain in patients with MI after they received other beta-blockers.<sup>13-15</sup>

Calcium antagonists have not been shown to reduce infarct size or mortality in acute MI and, in man, may even increase mortality. In a randomised study, 66 patients with acute MI received nifedipine or placebo about 4.5 hours after the onset of pain.<sup>39</sup> There was no difference in cumulative CK-MB levels between the two groups, indicating that nifedipine did not influence the extent of infarction.

Several other studies, in which nifedipine was administered early in acute MI, confirmed this observation.<sup>64-67</sup> Four studies showed that verapamil did not consistently reduce infarct size<sup>68-69</sup> or re-infarction rate.<sup>69,71</sup>

In the randomised study described above,<sup>39</sup> overall

of nifedipine and verapamil on mortality.<sup>64-65,72</sup> As a result, it has been concluded that, "Nifedipine did not affect the progression to acute infarction among the patients with threatened infarction nor did it alter infarct size. There was, in fact, a tendency to a higher mortality in the nifedipine-treated patients."<sup>73</sup>

There is also no convincing evidence that

inhibitors

---

## Continued beta-blockade protects against re-infarction

---

## Risks to the patient

Survivors of an acute infarction are at increased risk of developing further ischaemic events and death.<sup>74</sup>

31% if unstable angina develops.<sup>1</sup>

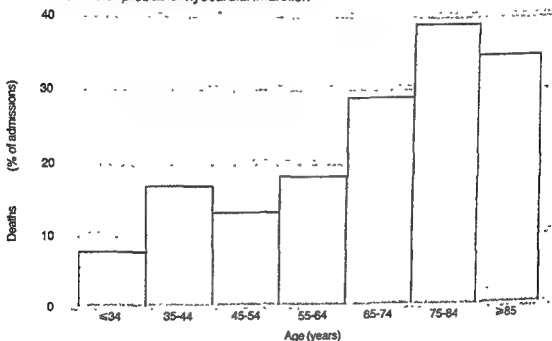
Angina developing post-infarct may also increase the risk of mortality.<sup>78-80</sup> During the first post-infarction year, there is a 10% mortality and in the subsequent 2-3 years, a 4% annual mortality.<sup>81</sup> About half of the post-hospital deaths are sudden (more than twice as common as non-sudden deaths<sup>4</sup>) and are mainly due to ventricular fibrillation.<sup>77</sup>

One year mortality increases again post-discharge for the age

probable MI ~

**Figure 8.**

The effect of age on in-hospital mortality from a definite or probable myocardial infarction



One year mortality increases again post-discharge for the age

public health terms<sup>3</sup> and should be distinguished from treatments which confer no material benefit. "Typically, treatment [with beta-blockade] of about 200 patients for one year . . . might be expected to avoid about 3 deaths and about 3 non-fatal reinfarctions."<sup>3</sup>

## 'Tenormin' – an effective treatment in post-infarct angina

As described in the 'Angina' chapter, 'Tenormin' is highly

effective than diltiazem or nifedipine<sup>86,87</sup> Therefore, 'Tenormin' can protect against the recurrence of angina in post-infarct patients

## Long-term benefit with beta-blockade

Pooling the results from long-term randomised studies yielded an extensive patient base of over 23,500. Analysis of the pooled mortality data demonstrated that

patients who were randomised to 'Tenormin' during the first week of treatment (11%, 2p<0.01) compared with the group who had received only normal coronary care

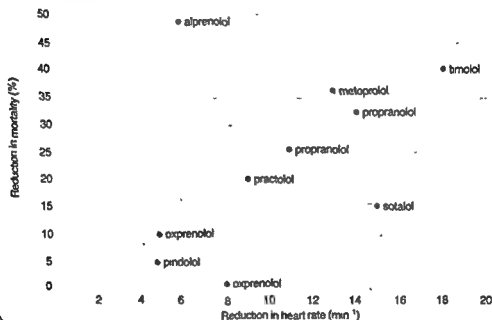
## beta-blocker after an infarction

The pooled results also showed that the

The extensive use of beta-blockers



**Figure 10.**  
Relationship between reduction in heart rate and reduction in mortality.



*almost linear relationship between the reduction in resting rate and mortality. The larger the reduction in heart rate, the larger is the reduction in*



## Long-term benefit from calcium antagonists

### Nifedipine

In long-term studies with nifedipine and verapamil alone

*calcium antagonists, there is no convincing evidence for secondary prevention.<sup>97</sup>*

The Secondary Prevention of Re-Infarction Nifedipine Trial (SPRINT) included 2279 survivors of an infarction

months of treatment, nifedipine did not significantly reduce mortality or non-fatal re-infarction.<sup>97</sup>

As mentioned earlier in this chapter, unlike 'Tenormin', nifedipine does not decrease heart rate and may even increase it.<sup>40</sup> A reflex increase in heart rate could, in certain cases, outweigh the benefit of a reduction in coronary artery tone.

### Verapamil

A total of 1436 patients admitted to coronary care units

## Summary: 'Tenormin' in acute myocardial infarction

- There is strong evidence that over-activation of the sympathetic nervous system is an important contributor to the development of an infarction
- Beta-blockade with 'Tenormin' offers protection against the consequences of excessive sympathetic discharge
- 'Tenormin' protects pre-infarct patients from developing a full MI
- 'Tenormin' saves lives in acute MI
- 'Tenormin' protects the heart at risk by reducing infarct size and reducing the incidence of arrhythmias

## References

- 2 YUSUFS, SLEIGHT P, ROSSI P *et al*  
Beta-blockade during and after myocardial infarction  
*Lancet* 1985, 2 57-66
- 3 ISIS COLLABORATIVE GROUP  
A randomised trial of intravenous atenolol among 16,027 cases of suspected acute myocardial infarction. ISIS-1  
*Lancet* 1985, 2 57-66
- 4 LURIA MH, DEBANNE SM and OSMAN MI  
Long-term follow-up after recovery from acute myocardial infarction. Observations on survival, ventricular arrhythmias, and sudden death  
*Arch Intern Med* 1985, 145 1592-95
- 5 YUSUFS, PETO R, LEWIS J, COLLINS R and SLEIGHT P  
Beta-blockade during and after myocardial infarction. An overview of the randomised trials  
*Prog Cardiovasc Dis* 1985, 27 (5) 333-71
- 6 JEWITT DE and SINGH BN  
The role of beta-adrenergic blockade in myocardial infarction  
*Prog Cardiovasc Dis* 1974, 16 421-38
- 7 HAN J  
Mechanisms of ventricular arrhythmia associated with myocardial infarction  
*Am J Cardiol* 1969, 24 800-13
- 8 MAROKO PR, KJEKSHUS JK, SOBEL BE *et al*  
Factors influencing infarct size following experimental coronary artery occlusions  
*Circulation* 1971, 43 67-82
- 9 KIRK ES and SONNENBLICK EH  
Newer concepts in the pathophysiology of ischemic heart disease  
*Am Heart J* 1982, 103 756-67
- 12 EPSTEIN SE and PALMERI ST  
Beta-blockade during and after myocardial infarction  
*Acta Med Scand* 1975, 587 (Suppl) 201-11
- 14 MIAMI TRIAL RESEARCH GROUP  
Metoprolol in acute myocardial infarction (MIAMI). A randomised placebo-controlled international trial  
*Eur Heart J* 1985, 6 199-226
- 15 GOLD HK, LEINBACH RC and MAROKO PR  
Propranolol-induced reduction of signs of ischemic injury during acute myocardial infarction  
*Am J Cardiol* 1976, 38 689-93
- 16 BOUDOULAS H, LEWIS RP, RITTIGERS SE, LEIER VC and VASKO JS  
Increased diastolic time. A possible important factor in the beneficial effect of propranolol in patients with coronary artery disease  
*J Cardiovasc Pharmacol* 1979, 1 503-13
- 17 LUDBROOK P, KARLINER JS, KOSTUCK W and O'ROURKE RA  
Effects of intravenously administered propranolol on wall motion abnormalities  
*Am J Cardiol* 1973, 31 712-17
- 18 HEIKKILÄ J and NIEMINEN MS  
Rapid monitoring of regional myocardial ischaemia with echocardiography and S-T segment shifts in man  
*Acta Med Scand* 1978, 623 (Suppl) 71-95
- 19 BATTLER A, ROSS J, SLUTSKY R, PFISTERER M, ASHBURN W and FROELICHER V  
Improvement of exercise-induced left ventricular dysfunction with oral propranolol in patients with coronary heart disease  
*Am J Cardiol* 1979, 44 318-24
- 20 MUELLER HS, AYERS SM, RELIGA A and EVANS RG  
Propranolol in the treatment of acute myocardial infarction. Effect on myocardial oxygen and haemodynamics  
*Circulation* 1974, 49 (6) 1078-87

22. OPIE LH and THOMAS M  
Propranolol and experimental myocardial infarction. Substrate effects  
*Postgrad Med J* 1976, 52 (Suppl 4) 124-32
23. OBEID A, SPEAR R, MOOKHERJEE S, WARNER R and EICH R  
Metabolic effects of propranolol on ischemic myocardium studied by regional sampling  
*Circulation* 1973, 48 (Suppl IV, Abstract 689) 174
24. HANEDA T, LEE T and GANZ W  
Metabolic effects of propranolol on ischemic myocardium studied by regional sampling  
*Circulation* 1973, 48 (Suppl IV, Abstract 689) 174
25. RELIGA A, MUELLER HS, EVANS R and AYERS SM  
Metabolic effect of propranolol on ischemic tissue in human and experimental myocardial infarction  
*Clin Res* 1973, 21 954
26. ROSSI PRF, YUSUFS, RAMSDALE D, FURZE L and SLEIGHT P  
Reduction of ventricular arrhythmias by early intravenous atenolol in suspected acute myocardial infarction  
*Br Med J* 1983, 286 506-10
27. RYDÉN L, ARNIEGO R, ARNMARK K *et al*  
A double-blind trial of metoprolol in acute myocardial infarction. Effects on ventricular tachycardia  
*N Engl J Med* 1983, 308 614-18
28. HOFFMAN BF and SINGER DH  
Appraisal of the effects of catecholamines on cardiac electrical activity  
*Ann NY Acad Sci* 1967, 139 914-39
29. ROBINSON C, BIRKHEAD J, CROOK B, JENNINGS K and JEWITT D  
Clinical electrophysiological effects of atenolol - a new cardioselective beta-blocking agent  
*Br Heart J* 1978, 40 14-21
30. DI BIASE M, FAVALE S and RIZZON P  
Electrophysiologic properties of intravenous 'Tenormin' in man  
*Eur J Cardiol* 1979, 2 (4) 333-42
31. SINGH BN and JEWITT DE  
Beta-adrenoreceptor blocking drugs in cardiac arrhythmias  
*Cardiovasc Drugs* 1977, 2 119-59
32. SINGH BN and JEWITT DE  
Challenge  
*Pharmacol Ther* 1981, 13 285-320
33. FRISHMAN WH, CHRISTODOULOU J, WEKSLER B, SMITHEN C, KILLIP T and SCHEIDT S  
Abrupt propranolol withdrawal in angina pectoris effects on platelet aggregation and exercise tolerance  
*Am Heart J* 1978, 95 169-79
34. KEBER I, JERSE M, KEBER D and STEGNAR M  
The influence of combined treatment with propranolol and acetylsalicylic acid on platelet aggregation in coronary heart disease.  
*Br J Clin Pharmacol* 1979, 7 287-91
35. KEBER I, JERSE M, KEBER D and STEGNAR M  
propranolol  
*Circulation* 1978, 58 (5) 881-86
36. O'ROURKE RA  
Symptoms of cardiovascular disease  
In: The American Heart Association Heartbook. New York. EP Dutton, 1980, 152-62
37. NORRIS RM, CLARKE ED, SAMMEL NL *et al*  
Protective effects of propranolol in threatened myocardial infarction  
*Lancet* 1978, 2 907-909
38. MULLER JE, MORRISON J, STONE PH *et al*  
Nifedipine therapy for patients with threatened myocardial infarction
39. MULLER JE, TURI ZG, PEARLE DL *et al*  
Nifedipine and conventional therapy for unstable angina pectoris. A randomized, double-blind comparison  
*Circulation* 1984, 69 (4) 728-39
40. LUBSEN J  
Unstable angina - a review of recent studies  
Paper presented at 'Cardioprotection in Ischaemic Heart Disease' Symposium, Basle, January 18th, 1986
41. WILCOX RG, HAMPTON JR, BANKS DC *et al*  
Trial of early nifedipine treatment in patients with suspected myocardial infarction (the TRENT study)  
*Br Heart J* 1986, 55 (5) 506

- 43 HAMPTON J  
Prognosis in ischaemic heart disease  
*Med Int* 1985, 2 (20) 832-37
- 45 SOBEL BE, BRESNAHAN GF, SHELL WE and YODER RD.  
Estimation of infarct size in man and its relation to prognosis  
*Circulation* 1972, 46 640-48
- 47 HAMPTON J  
Prognosis in ischaemic heart disease  
*Circulation* 1979; 59 113-19
- 48 KHAN MIG  
Beta-adrenoceptor blockers.  
In *Manual of Cardiac Drug Therapy* London  
Baillière Tindall, 1984, 16-33
- 49 SLOMAN G, ROBINSON JS and McLEAN K.  
Propranolol ('Inderal') in persistent ventricular fibrillation.  
*Br Med J* 1965, 1 895-96
- 50 KERNOHAN RJ  
Management of arrhythmias in acute myocardial infarction  
*Insh J Med Sci* 1967, 6 257-68
- 51 IKRAM H  
Propranolol in persistent ventricular fibrillation complicating acute myocardial infarction  
*Am Heart J* 1968, 75 795-96
- 52 GIBSON D and SOWTON E  
The use of beta-adrenergic receptor blocking drugs in dysrhythmias.  
*Prog Cardiovasc Dis* 1969, 12 (1) 16-39
- 53 JEWITT M and CROXSON R.  
Practolol in the management of cardiac dysrhythmias following myocardial infarction and cardiac surgery  
*Postgrad Med J* 1971, 47 25-29
- 54 LEMBERG L, CASTELLANOS A and ARCEBAL AG  
The use of propranolol in arrhythmias complicating acute myocardial infarction  
*Am Heart J* 1970; 80 479-87
- 55 LEMBERG L, ARCEBAL AG  
The use of propranolol in arrhythmias complicating acute myocardial infarction  
*Am Heart J* 1970; 80 479-87
- 59 NORRIS RM, BROWN MA, CLARKE ED *et al*  
Prevention of ventricular fibrillation during acute myocardial infarction by intravenous propranolol  
*Lancet* 1984, 2 883-86
- 60 AHUMADA GG, KARLSBERG RP, JAFTE AS, AMBOS HD, SOBEL BE and ROBERTS R.  
Reduction of early ventricular arrhythmia by acebutolol in patients with acute myocardial infarction  
*Br Heart J* 1979; 41 654-59
- 61 OLSSON G, REHNQVIST N, LUNDMAN T and MELCHER A.  
Metoprolol treatment after acute myocardial infarction. Effects on ventricular arrhythmias and exercise tests during 6 months  
*Acta Med Scand* 1981, 210 (1-2) 59-65
- 62 HJALMARSON A, ELMFELDT D, HERLITZ J *et al*  
Effect on mortality of metoprolol in acute myocardial infarction. A double-blind randomized trial  
*Lancet* 1981, 2 823-27
- 63 KHAN MIG  
Management of acute myocardial infarction  
In *Manual of Cardiac Drug Therapy* London  
Baillière Tindall, 1984, 99-125
- 64 SIRNES PA, OVERSKJED K, PEDERSEN TR *et al*  
Evolution of infarct size during the early use of nifedipine in patients with acute myocardial infarction. The Norwegian Nifedipine Multicenter Trial.  
*Circulation* 1984, 70: 638-44

- 65 GOTTlieb SO, WEISS JJ, FLAHERTY JT *et al*.  
Effect of nifedipine on clinical course and left  
ventricular function in low risk acute myocardial  
infarction. A double-blind randomised trial  
*Circulation* 1984, 70 (Suppl II, Abstract 1028)  
257
- 66 LOOGNA E, SYLVÉN G, GROTH T and  
MOGENSEN L  
Complexity of enzyme release during acute  
myocardial infarction in a controlled study with  
early nifedipine treatment  
*Eur Heart J* 1985, 6 114-19
- 67 EISENBERG PR, LEE RG, BIELLO DR,  
GELTMAN EM and JAFFE AS  
Chest pain after nontransmural infarction. The  
absence of remediable coronary vasospasm  
*Am Heart J* 1985, 110 515-21
- 68 THUESEN L, JORGENSEN JR,  
KVISTGAARD HJ *et al*  
Effect of verapamil on enzyme release after early  
intravenous administration in acute myocardial  
infarction. Double-blind randomised trial  
*Br Med J* 1983, 286 1107-108
- 69 CREA F, DEANFIELD J, CREA P,  
SHAROM M, DAVIES G and MASERI A.  
Effects of verapamil in preventing early  
postinfarction angina and reinfarction  
*Am J Cardiol* 1985, 55 900-904
- 70 BUSSMANN W-D, SEHER W, GRÜNGRAS M,  
KLEPZIG H and KALTENBACH M  
Reduction of CK and CKMB indexes of infarct  
size by intravenous verapamil  
*Circulation* 1982, 66 (Part II) Abstract 8
- 71 MASERI A.  
Unstable angina. In Maseri A and Goodwin JF,  
eds. *Hammersmith Cardiology Workshop Series*  
Vol 1. New York. Raven Press, 1984, 169-74
- 72 DANISH MULTICENTER STUDY GROUP ON  
VERAPAMIL IN MYOCARDIAL  
INFARCTION  
Verapamil in acute myocardial infarction  
*Am J Cardiol* 1984, 54 24E-28E
- 74 FRISHMAN WH and RIBNER H  
A modern approach to an old problem  
*Am J Cardiol* 1979, 43 1207-13
- 75 OLIVER MF, HEADY JA, MORRIS JN and  
COOPER J
- 76 MAY GS, EBERLEIN KA, FURBERG CD,  
PASSAMANI ER and DeMETS DL.  
Secondary prevention after myocardial infarction  
A review of long-term trials  
*Prog Cardiovasc Dis* 1982, 24 331-52
- 77 FRISHMAN WH, FURBERG CD and  
FRIEDEWALD WT.  
The use of beta-adrenergic blocking drugs in  
patients with myocardial infarction  
*Curr Probl Cardiol* 1984, 9 (3) 1-50
- 78 MOSS AJ, DeCAMILLA J, DAVIS H and  
BAYER L.  
The early posthospital phase of myocardial  
infarction.  
*Circulation* 1976, 54 58-64
- 79 SCHUSTER EH and BULKLEY BH
- 80 TAYLOR GJ, HUMPHRIES JO,  
MELLITS ED *et al*.  
Predictors of clinical course, coronary anatomy  
and left ventricular function after recovery from  
acute myocardial infarction  
*Circulation* 1980, 62 960-70
- 81 WEINBLATT E, SHAPIRO S, FRANK CW  
*et al*.  
Prognosis of men after first myocardial infarction  
Mortality and first recurrence in relation to  
selected parameters  
*Am J Public Health* 1968, 58 1329-47
- 82 WELD FM, CHU KL, BIGGER JT and  
ROLNITZKY LM  
Risk stratification with low-level exercise testing  
two weeks after acute myocardial infarction  
*Circulation* 1981, 64 306-14
- 83 GELTMAN EM, EHSANI AA, CAMPBELL MK,  
SCHECHTMAN K, ROBERTS R and  
SOBEL BE  
The influence of location and extent of myocardial  
infarction on long-term ventricular dysrhythmia  
and mortality  
*Circulation* 1979, 60 805-14
- 84 FURBERG C, MORTON-HAWKINS C and  
LICHSTEIN E  
Effects of propranolol in post-infarction patients  
with mechanical or electrical complications  
*Circulation* 1984, 69 761-65
- 85 LESSEM J  
Combined therapy with Ca-antagonists and beta-  
adrenergic receptor blocking agents in chronic  
stable angina.  
*Acta Med Scand* 1984, 215 (Suppl 681) 83-90

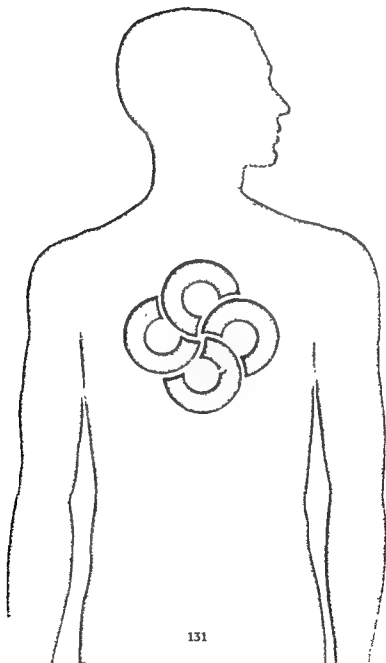
- 86 BERTHOUD P, RASSAND J, SCHIPMAN C  
et al  
Comparative anti-ischaemic activity of atenolol  
and diltiazem. A randomized, single-blind, cross-  
over study using computerized exercise tests  
*Rev Med Int* 1985, 6: 259-65
- 87 de BUTTEIR M, ROWLAND E and  
KRIKLER DM  
Hemodynamic effects of nifedipine given alone  
and in combination with atenolol in patients with  
impaired left ventricular function  
*Am J Cardiol* 1985, 55 (12): 15E-20E.
- 88 NORRIS RM  
 $\beta$ -Adrenoceptor blockers. An update of their role  
in acute myocardial infarction.  
*Drugs* 1985, 29: 97-104
- 89 HAWKINS CM, RICHARDSON DW and  
VOKONAS IS  
Effect of propranolol in reducing mortality in older  
myocardial infarction patients. The Beta-Blocker  
Heart Attack Trial Experience  
*Circulation* 1983, 67 (Suppl I): 1-94-1-97
- 90 RHODDA BE.  
The timolol myocardial infarction study:  
An evaluation of selected variables.  
*Circulation* 1983, 67 (Suppl II): 1-101-1-106
- 91 KJEKSHUS J  
Comments - Beta-blockers. Heart rate reduction a  
mechanism of benefit.  
*Eur Heart J* 1985, 6 (Suppl A): 29-30
- 92 QUYYUMI AA, WRIGHT C, MOCKUS L and  
FOX KM  
Effect of partial agonist activity in  $\beta$ -blockers in  
severe angina pectoris: a double-blind comparison  
of pindolol and atenolol  
*Br Med J* 1984, 289: 931-33
- " . . . . .  
. . . . .  
N Engl J Med 1982, 307: 1293-301
- 94 EUROPEAN INFARCTION STUDY GROUP  
A secondary prevention study with slow-release  
oxprenolol after myocardial infarction: morbidity  
and mortality  
*Eur Heart J* 1984, 5: 189-202
- 95 AUSTRALIAN and SWEDISH PINDOLOL  
STUDY GROUP  
The effect of pindolol on the two years mortality  
after complicated myocardial infarction  
*Eur Heart J* 1983, 4: 367-75
- 96 OWENBY DA and O'ROURKE MF.  
Failure of intravenous pindolol to reduce the  
hemodynamic determinants of myocardial oxygen  
demand or enzymatically determined infarct size  
in acute myocardial infarction.  
*Aust NZ J Med* 1985, 15 (6): 704-11
- 97 BÖHLER FR, MÜLLER FB, LINDER L and  
BOLLI P  
Antihypertensive therapy and myocardial  
infarction. Focus on calcium antagonists  
*J Hypertension* 1985, 3 (Suppl 2): S95-S98



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## Drug interactions with 'Tenormin'

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## References 147

## General principles

combined medication.

proportion of the parent compound needs to be metabolised before changes in blood levels and potential clinical symptoms become evident.

**Table 1. Some factors affecting drug pharmacokinetics.**

Common factors affecting drug pharmacokinetics	Pharmacokinetic parameter influenced:			
	Absorption	Distribution	Metabolism	Excretion
Water/lipid solubility	+	+	+	+
Blood flow:				
gastrointestinal tract	+			
cardiac output		+		
liver			+	
kidney				+
Competition for:				
absorbing site	+			
protein binding site		+		
metabolising site			+	
tubule secreting site				+
Organ function	+		+	+
Other factors:				
Physicochemical properties of drug	+			
Enzyme induction			+	
Enzyme inhibition			+	

Drug blockers may be eliminated from the body.

enzymes of the cytochrome P<sub>450</sub> system. Plasma levels of drug and/or metabolite may be affected if two drugs

## **Lipid solubility – an important determinant of pharmacokinetic interactions**

The second type – pharmacodynamic interactions – are generally more predictable provided the pharmacology of the drugs is known and may include haemodynamic and electrophysiological mechanisms. Hepatic drug metabolism is also dependent on hepatic blood flow which, if altered, may affect plasma drug levels by changing the rate of drug presentation to the metabolising enzymes.

Whilst the cardioselectivity of beta-blockers does not appear to be an important factor in determining drug interactions, lipid solubility is of characteristic importance. The water/lipid solubility of a beta-blocker

is found to be an important determinant of its

DIURETIC

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## **Which drugs interact with ‘Tenormin’?**

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The results of trials designed to investigate the drugs with

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## **Calcium antagonists**

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can be associated with

**Table 2. Effect of co-prescribed drugs on 'Tenormin'.**

Drug	Effect on 'Tenormin'	Relevant clinical effects	Reference
Acetylsalicylic acid	None	None	31
Alcohol	None	None	55,56
Allopurinol	None	None	31
Aluminium hydroxide	Decreased bioavailability	None	8,50
Amitriptyline	None	None	54
Ampicillin	Decreased bioavailability	Unknown	31,59
Calcium	Decreased bioavailability	None	8
Chlorthalidone	None	Enhanced b p. reduction	6,7
Cimetidine	None	None	38,40,65
Diazepam	None	None	52
Flurbiprofen	None	None	36
Food	Decreased bioavailability	None	62
Fruzemide	None	None	8
Hydralazine	None	None	9
Indomethacin	Unknown	Increase in b p.	32
Isosorbide dinitrate	None	None	12
Metoclopramide	None	None	50
Nifedipine	None	Enhanced b p. reduction	2,66
Propantheline	Increased bioavailability	None	50
Ranitidine	None	None	38,45
Smoking	None	None	3
Sulindac	Unknown	None	32

b p. = blood pressure

## Nifedipine

As it is also relevant to know if the two types of agent interact pharmacokinetically, the disposition of 'Tenormin' metoprolol and atenolol were each

examined in a study by the authors. The results are shown in Table 3.

Approximately, one hour after the administration of 20 mg

of metoprolol, the plasma concentration of the drug was 1.5 µg/ml.

After the administration of 20 mg of atenolol, the plasma concentration of the drug was 1.5 µg/ml.

The results of the study are shown in Table 3.

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**Table 3. Effect of 'Tenormin' on other drugs.**

Drug	Effect of 'Tenormin' on other drug	Relevant clinical effects	Reference
Acenocoumarin	Unknown	None	18
Alcohol	None	None	55,56
Antipyrine	None	None	30
Disopyramide	Decreased clearance	Unknown	28
7-Ethoxycoumarin	None	None	13
Isosorbide dinitrate	None	None	12
Lignocaine	None	None	20
Phenprocoumon	None	None	17
Tolbutamide	None	None	20
Verapamil	None	None	4
Warfarin	Increased peak blood levels	None	14

## Verapamil

Verapamil has no effect on the pharmacokinetics of

in patients with impaired ventricular function, and this combination should not be given to patients with conduction abnormalities (see Prescribing Information).

There is no evidence of increased myocardial

## Diuretics – complementary action particularly useful in hypertension

### Chlorthalidone

The antihypertensive effect of fixed combinations of 'Tenormin' with chlorthalidone ('Tenoretic' and 'Tenoretic') is to be equivalent to the free

There is no evidence of a pharmacokinetic interaction in hypertensive

### Frusemide

Frusemide has no effect on the bioavailability of 'Tenormin'.<sup>8</sup>

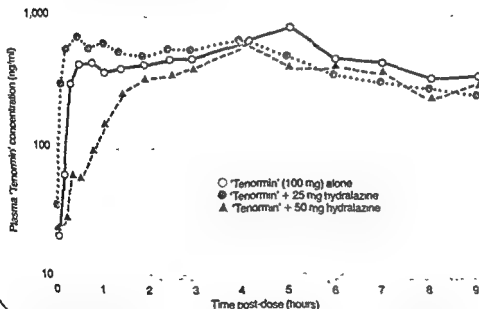
## Vasodilators -- no effect on 'Tenormin' kinetics

### Hydralazine

The pharmacokinetics of 100mg 'Tenormin' were unaffected by concurrent oral administration of 25 or

changes rather than a metabolic interaction<sup>11</sup>

Figure 1.  
Effect of oral administration of hydralazine on  
plasma concentrations of 'Tenormin'



### Isosorbide dinitrate

Neither 'Tenormin' nor isosorbide dinitrate had any effect on the pharmacokinetics of each other.<sup>12</sup>

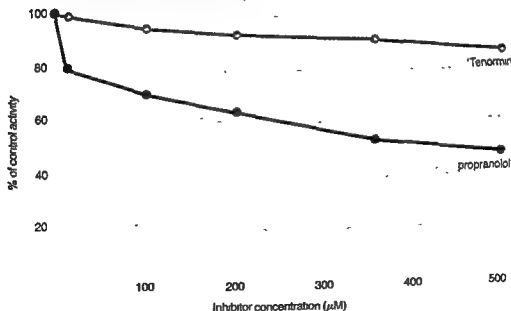
## Anticoagulant status unaffected by 'Tenormin'

A further potentially important source of drug interactions is the co-administration of beta-blockers with anticoagulants, eg in patients with myocardial infarction. 'Tenormin' does not display any adverse clinical sequelae when administered with anticoagulants.

### 7-Ethoxycoumarin

Using *in vitro* preparations of hepatic microsomal enzymes, 'Tenormin', unlike propranolol, did not inhibit 7-ethoxycoumarin metabolism<sup>15</sup> (Figure 2). The

Figure 2.  
Effect of propranolol and 'Tenormin' on  
7-ethoxycoumarin deethylase activity



## Warfarin

The effect of metoprolol on Factor VIII activity of normal subjects was studied by a group of investigators from the University of Toronto.<sup>14</sup> They found that metoprolol had no effect on Factor VIII activity. However, other work has shown that metoprolol does not affect the anticoagulant activity of warfarin.<sup>15</sup>

## Phenprocoumon

In a study done in healthy subjects, 'Tanonin' did not affect the anticoagulant activity of phenprocoumon. On phenprocoumon, the investigators related, *"Although the transient increase of phenprocoumon plasma levels caused by metoprolol may be of little clinical significance after a single dose of phenprocoumon, a more important alteration in phenprocoumon disposition and effect should be expected in long-term treatment of long-term therapy."*<sup>16</sup>

## Acenocoumarin

The activity of acenocoumarin, in patients receiving this drug for the long-term treatment of

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## Anti-arrhythmic agents – more evidence required

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## Lignocaine

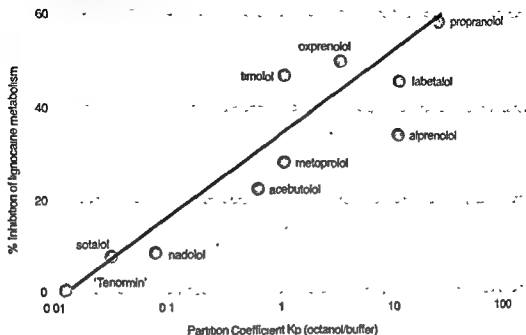
As a result of the low therapeutic index of lignocaine, it

(Figure 3)

As a result of the low therapeutic index of lignocaine, it may exhibit toxicity if plasma levels increase above normal. This is particularly relevant to post-infarction patients.



**Figure 3.**  
Relationship between % inhibition of lignocaine metabolism  
by rat liver microsomes for different  $\beta$ -blockers<sup>19</sup>



## Disopyramide

Disopyramide is a class II antiarrhythmic agent.

are conflicting.<sup>24-27</sup>

The elimination half-life of disopyramide was measured after

The clearance of disopyramide was

to be taken when

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## **Anti-inflammatory and analgesic agents -- a possible interaction with beta-blockers?**

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### **Antipyrine**

Preliminary work indicated that there was no difference

standard once-daily dose of 100mg 'Tenormin' had no effect on the clearance, volume of distribution and elimination half-life of antipyrine in normal volunteers<sup>30</sup>

significantly lowered the mean plasma clearance of antipyrine at equal degrees of beta-blockade

### **Acetylsalicylic acid**

In healthy volunteers, 500mg acetylsalicylic acid did not alter the pharmacokinetics of 'Tenormin'.<sup>31</sup>

### **Indomethacin, sulindac**

Indomethacin appears to increase blood pressure in hypertensive patients treated with different beta-blockers including 'Tenormin', oxprenolol, pindolol and propranolol,<sup>32-35</sup> but this property is not shared with the anti-inflammatory agent, sulindac.<sup>32</sup> The speculated pharmacodynamic mechanism may involve opposing effects on systemic and/or renal prostaglandins.<sup>32</sup>

### **Flurbiprofen**

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## **Histamine (H<sub>2</sub>)-receptor blockers -- concurrent use with certain lipophilic beta-blockers may cause problems**

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solution to the problem as it has not been shown to interact with this class of drug

Tenormin' was not affected by co-administration of cimetidine, probably by inhibition of the drug metabolism.

Tenormin' was not affected by co-administration of cimetidine.

by biotransformation,<sup>38</sup> or penbutolol, which is mainly eliminated by phase II reactions such as glucuronidation.<sup>38</sup>

Cimetidine pharmacokinetics were unaffected by beta-blocker administration.<sup>38</sup>

**Table 4. Beta-blocker/cimetidine interactions<sup>38</sup>**  
(Drugs administered for 7 days to 6 patients)

Treatment		Peak plasma conc (ng ml <sup>-1</sup> )	AUC (ng ml <sup>-1</sup> h)	Elimination half-life (h)
Metoprolol 100 mg bid	Alone	177	1,167	4.4
	Plus cimetidine	284*	1,885*	7.0
Propranolol 80 mg bid	Alone	126	948	5.6
	Plus cimetidine	251*	2,112*	7.6
'Tenormin' 100 mg daily	Alone	660	5,787	7.4
	Plus cimetidine	610	5,827	7.5

\* =  $p < 0.05$

No pharmacodynamic interaction was reported in

Ranitidine

There is no significant interaction between ranitidine and 'Tenormin'.  
clarification.

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### Other anti-ulcer drugs – no clinically important interaction with 'Tenormin'

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Aluminium hydroxide

Aluminium hydroxide reduced the bioavailability of 'Tenormin' by 50%  
due to an increase in gastric pH affecting the dissolution rate of 'Tenormin'.<sup>50</sup>

Propantheline

Propantheline has no effect on the bioavailability of 'Tenormin'.  
It is unlikely to affect the degree of beta-blockade by 'Tenormin' in view of its flat dose-response curve.

Metoclopramide

Metoclopramide increases the rate of gastric emptying but has no effect on the bioavailability of 'Tenormin'.<sup>50</sup>

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### Psychotropic drugs – no interaction with 'Tenormin'

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Diazepam

Metoprolol has no effect on the bioavailability of diazepam.  
propranolol, but not by 'Tenormin'.<sup>51,52</sup> The increased plasma levels of diazepam and metabolites produced by the lipophilic beta-blockers were closely associated with an impairment of psychomotor performance.<sup>52</sup>

'Tenormin' did not impair subjects' psychomotor function even when administered with diazepam. Hawksworth and colleagues noted that when diazepam needs to be given with a beta-blocker, "... use of a hydrophilic  $\beta$ -adrenoceptor antagonist would appear to minimise the incidence of adverse side effects."<sup>52</sup>

Other aspects of the psychomotor testing carried out in this study are described in the 'Hydrophilicity' chapter

## Amitriptyline

In healthy subjects who received 'Tenormin' or metoprolol in combination with amitriptyline, there was

The pharmacokinetics of 'Tenormin' were not altered by amitriptyline.

## Alcohol

Alcohol ingestion activated propranolol metabolism,<sup>56</sup>

The pharmacokinetics of 'Tenormin' were unchanged by alcohol ingestion and *vice versa*.<sup>55,56</sup>

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## Smoking has less effect on 'Tenormin' than on lipophilic beta-blockers

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## Cigarette smoking

In addition to increasing heart rate and blood pressure,<sup>57</sup> cigarette smoking may also induce liver drug

less  
3

of propranolol and nifedipine were lower in patients on enalapril than in patients off enalapril but the difference was not significant.<sup>58</sup>

**Table 5. Area and severity of S-T segment depression measured immediately after exercise<sup>5</sup>**

		Smoking	No Smoking
Placebo	area	5.6 ± 3.2	4.1 ± 3.2
	severity	6.8 ± 4.0	5.4 ± 3.4
'Tenormin'	area	2.0 ± 1.8	1.4 ± 1.4
	severity	2.5 ± 2.6	1.7 ± 1.7
Propranolol	area	2.6 ± 2.0	1.9 ± 2.0
	severity	3.4 ± 2.7	2.5 ± 3.2
Nifedipine	area	3.9 ± 3.0	2.1 ± 2.8
	severity	5.3 ± 2.8	2.5 ± 3.3

## Miscellaneous agents

### Ampicillin

antibiotics are known to impair drug absorption,<sup>60,61</sup> the mechanism may involve a decrease in the

tenormin was unchanged in hypertensive patients receiving the same drug combination.<sup>31</sup>

## Food

Under normal conditions, 'Tenormin' is only about 50% absorbed due to its hydrophilic nature (see 'Pharmacokinetics' chapter). Ingestion of food reduced the absorption of 'Tenormin' by approximately 20% but this was not thought to have any clinically relevant consequences.<sup>62</sup>

In direct contrast, the bioavailability of metoprolol and propranolol were enhanced by food intake probably due

## Calcium

Calcium antagonists have been used in combination with 'Tenormin' in the treatment of hypertension. In a study of 12 patients with essential hypertension, the combination of 'Tenormin' and nifedipine was found to be more effective than either drug alone in lowering blood pressure.

normal subjects experienced a reduction in exercise tachycardia. Nevertheless, blood pressure control was unimpaired in hypertensive patients receiving the same combination.<sup>8</sup>

## Allopurinol

In healthy volunteers, allopurinol had no demonstrable effect on the pharmacokinetics of 'Tenormin'.<sup>31</sup>

## Tolbutamide

The bioavailability and clearance of tolbutamide in normal volunteers was unaffected by 'Tenormin'.<sup>80</sup>

## Summary: Drug interactions with 'Tenormin'

- Consistent pharmacokinetics enable prediction of possible drug interactions
- Beneficial pharmacodynamic interactions with diuretics and some calcium antagonists confer important therapeutic advantages for patients
- Hydrophilic molecule means few liver-mediated drug interactions
- Unlike lipophilic beta-blockers, 'Tenormin' kinetics are unaffected by cimetidine and hydralazine
- Less affected by enzyme inducer, nicotine, than lipophilic beta-blockers
- Bioavailability altered only by a small number of agents usually without adverse clinical sequelae
- Caution may be necessary if patients are also taking verapamil or disopyramide

# References

- 1 McDEVITT DG  
Drug interactions involving beta-adrenoceptor blocking drugs.  
*Cardiovascular and Respiratory Disease Therapy: Clinically Important Adverse Drug Interactions* 1980; 1: 21-41
- 2 GANGJI D, JUVENT M, NISSET G *et al*  
Study of the influence of nifedipine on the pharmacokinetics and pharmacodynamics of propranolol, metoprolol and atenolol  
*Br J Clin Pharmacol* 1984; 17 (Suppl 1): 29s-35s
- 3 FOX KM, DEANFIELD J, KRIKLER S, RIBEIRO P and WRIGHT C  
The influence of cigarette smoking on the medical management of angina.  
*Drugs* 1983; 25 (Suppl 2): 177-80
- 4 and propranolol  
*Br J Clin Pharmacol* 1984; 17 (Suppl 1): 37s-44s.
- 5 FREEMAN D, DI-PIETRO L and CARRUTHERS G  
Influence of verapamil on the acute and chronic  
*Drugs* 1983; 25 (Suppl 2): 177-80
- 6  
*Eur J Clin Pharmacol* 1980; 17: 333-37
- 7 McAINSH J, BASTAIN W, YOUNG J and HARRY JD  
Bioavailability in man of atenolol and chlorthalidone from a combination formulation  
*Biopharm Drug Dispos* 1981; 2: 147-56
- 8 KIRCH W, SCHÄFER-KÖRTING M, AXTHELM T, KÖHLER H, and MUTSCHLER E  
Interaction of atenolol with furosemide and calcium and aluminum salts  
*Clin Pharmacol Ther* 1981; 30 (4): 429-35
- 9 McLEAN AJ, WILHELM D and HEINZOW BG  
Stable oral availability of atenolol co-administered with hydralazine. Comparison with propranolol, metoprolol and other beta-adrenoceptor antagonists.  
*Drugs* 1983; 25 (Suppl 2): 131-35
- 10 McLEAN AJ, SKEWS H, BOBIK A and DUDLEY FJ  
Interaction between oral propranolol and hydralazine  
*Clin Pharmacol Ther* 1980; 27: 726-32
- 11 HAWKSWORTH GM, DART AM, CHIANG CS, PARRY K and PETTIE JC  
Effects of oxprenolol on the pharmacokinetics and pharmacodynamics of hydralazine  
*Drugs* 1983; 25 (Suppl 2): 136-40
- 12 BOGAERT MG, ROSSEEL MT and LEBEVRE RA  
Lack of pharmacokinetic interaction between isosorbide dinitrate and the beta adrenergic receptor blockers atenolol and propranolol  
*Br J Clin Pharmacol* 1984; 17 (Suppl 1): 90s-91s.
- 13 AHOKAS JT, DAVIES C and RAVENSCROFT PJ  
Comparison of  $\beta$ -adrenoceptor antagonists as modulators of drug metabolism. Effect of lipophilicity on microsomal phase I and II reactions  
*Br J Clin Pharmacol* 1984; 17 (Suppl 1): 103s-105s
- 14 BAX NDS, LENNARD MS, TUCKER GT *et al*  
The effect of beta-adrenoceptor antagonists on the pharmacokinetics and pharmacodynamics of warfarin.  
*Br J Clin Pharmacol* 1984; 17 (Suppl 1): 85s
- 15 SCOTT AK, PARK BK and BRECKENRIDGE AM  
Interaction between warfarin and propranolol.  
*Br J Clin Pharmacol* 1984; 17 (Suppl 1): 86s
- 16  
antagonists  
*Drugs* 1983; 25 (Suppl 2): 121-26
- 17 SPAHN H, KIRCH W, MUTSCHLER E *et al*  
Pharmacokinetic and pharmacodynamic interactions between phenprocoumon and atenolol or metoprolol  
*Br J Clin Pharmacol* 1984; 17 (Suppl 1): 97s-102s
- 18  
*Br J Clin Pharmacol* 1981; 12: 429-31



- 20 WING LMH, MINERS JO, HARRINGTON BJ, LILLYWHITE K and SMITH KJ

Pharmacologists, 13-15th December, 1982, Sydney 65

- 21 CONRAD KA, BYERS JM, FINLEY PR and BURNHAM L  
Lidocaine elimination Effects of metoprolol and of propranolol  
*Clin Pharmacol Ther* 1983, 33 133-38

- 23 GRAHAM CF, TURNER WM and JONES JK  
Lidocaine-propranolol interactions  
*N Engl J Med* 1981 304 1301

- 24 CUMMING AD and ROBERTSON C  
Interaction between disopyramide and practolol  
*Br Med J* 1979, 2 (6200) 1264

- 26 CATHCART-RAKE WF, COKER JE, ATKINS FL *et al.*  
The effect of concurrent oral administration of propranolol and disopyramide on cardiac function in healthy men  
*Circulation* 1980, 61 (5) 938-45

- 27 IKRAM H

- 30 TUCKER GT, BAX NDS, LENNARD MS, CREWE K and WOODS HF  
Lack of effect of atenolol on antipyrine clearance  
*Br J Clin Pharmacol* 1982, 14 743-44

*Clin Pharmacol Ther* 1983, 33 (3) 283-88

some pharmacological actions of atenolol in hypertensive patients  
*Br J Clin Pharmacol* 1984, 17 (Suppl 1) 108s-111s.

- 33 SALVETTI A, ARZILLI F, PEDRINELLI R, BEGGI P and MOTOLESE M  
Interaction between oxprenolol and indomethacin on blood pressure in essential hypertensive patients  
*Eur J Clin Pharmacol* 1982, 22 197-201

- 34 DURAO U and RICO GT  
Modification by indomethacin of the blood pressure lowering effect of pindolol and propranolol in conscious rabbits  
*Eur J Pharmacol* 1977, 43 377-81

- 35 LOPEZ-OVEJERO JA, WEBER MA, DRAYER JJ, SEALEY JE and LARAGH JH  
Effects of indomethacin alone and during diuretics or beta-adrenoceptors blockade therapy on blood pressure and the renin system in essential hypertension  
*Clin Sci Mol Med* 1978, 55 203s-205s

- 36 WEBSTER J, PETRIE JC, McLEAN J and HAWKSWORTH GM  
Flurbiprofen interaction with single doses of atenolol and propranolol  
*Br J Clin Pharmacol* 1984, 18 661-66

- 37 GREENE W  
Drug interactions involving cimetidine - mechanisms, documentation, implications  
*Rev Drug Metab Drug Interactions* 1984, 5 (1) 25-51

- 41 ELLIS ME, HUSSAIN M, WEBB AK, BARKER

- 42 FEELY J, WILKINSON GR and WOOD AJJ  
Cimetidine administration results in increased effects of propranolol and higher propranolol blood levels  
*Circulation* 1980, 62 (4) Abstract 982

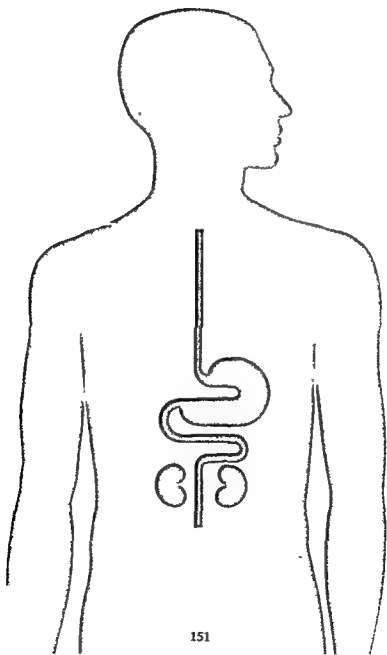
- 11 DONOVAN MA, HILAGERTY AM, PATEL L, CASTLEDEN M and POHL JEF  
Cimetidine and bioavailability of propranolol  
*Lancet* 1981; 1 164
- 44 DANESHMEND TK and ROBERTS CJC  
Cimetidine and bioavailability of labetalol  
*Lancet* 1981; 1 (8219) 565
- 45 SPAHN H, MUTSCHLER E, KIRCH W, OHNHAUS E and JANISCH HD  
Influence of ranitidine on plasma metoprolol and atenolol concentrations.  
*Br Med J* 1983; 286 (6377) 1546-47
- 46 KELLY JG, SHANKS RG and McDEVITT DG  
Influence of ranitidine on plasma metoprolol concentrations.  
*Br Med J* 1983; 287 (6400) 1218-19
- 47 JACK D, MITCHARD M and SMITH RN  
Influence of ranitidine on plasma metoprolol concentrations.  
*Br Med J* 1983; 286 (6383) 2004
- 48 JACK D, MITCHARD M and SMITH RN  
Influence of ranitidine on plasma metoprolol concentrations.  
*Br Med J* 1983; 287 (6400) 1218
- 49 DOBBS JH, SKOUTAKIS VA, ACCHIARDO SR and DOBBS BR  
Effects of aluminum hydroxide on the absorption of propranolol.  
*Curr Ther Res* 1977; 21 887-92.
- 50 REGÄRDH CG, LUNDBORG P and PERSSON BA  
The effect of antacid, metoclopramide and propantheline on the bioavailability of metoprolol and atenolol.  
*Biopharm Drug Dispos* 1981; 2 79-87
- 51 BETTS T, CROWE A and HAWKSWORTH G  
Diazepam/beta-adrenoceptor antagonist interactions  
*Br J Clin Pharmacol* 1984; 17 (Suppl. 1) 69s-76s
- 52 HAWKSWORTH G, BETTS T, CROWE A *et al*  
Diazepam/beta-adrenoceptor antagonist interactions  
*Br J Clin Pharmacol* 1984; 17 (Suppl. 1) 69s-76s
- 53 KIRCH W, SPAHN H, HUTT HJ, OHNHAUS EE and MUTSCHLER E  
Interaction between alcohol and metoprolol or atenolol in social drinking.  
*Drugs* 1983; 25 (Suppl 2) 152.
- 56 RAUTIO A, ANTILA M, STENGARD JH, JARVENSIVU P, KARVONEN JT and SOTANIEMI EA  
Alcohol and beta-blocking interactions  
*Acta Pharmacol Toxicol* 1981; 49 (Suppl. 1) 73
- 57 ORAM S and SOWTON E  
Tobacco angina.  
*Q J Med* 1963; 32 115-43
- 58 VESTAL RE, WOOD AJJ, BRANCH RA, SHAND DG and WILKINSON GR  
Effects of age and cigarette smoking on propranolol disposition.  
*Clin Pharmacol Ther* 1979; 26 (1) 8-15
- 59 McLEAN AJ, TONKIN A, MCCARTHY P and HARRISON P  
Dose-dependence of atenolol-ampicillin interaction  
*Br J Clin Pharmacol* 1984; 18 969-71
- 60 FALOON WW  
Drug production of intestinal malabsorption.  
*NY State J Med* 1970; 70 2189-92.
- 61 TOSKES PP and DEREN JJ  
Selective inhibition of vitamin B<sub>12</sub> absorption by para-aminosalicylic acid.  
*Gastroenterology* 1972; 62 1232-37
- 62 MELANDER A, STENBERG P, LIEDHOLM H, SCHERSTEN B and WAHLIN-BOLL E  
Food-induced reduction in bioavailability of atenolol.  
*Eur J Clin Pharmacol* 1979; 16 327-30
- 63 HOUTZAGERS JJR, STREURMAN O and REGÄRDH CG  
The effect of pretreatment with cimetidine on the bioavailability and disposition of atenolol and metoprolol.  
*Br J Clin Pharmacol* 1982; 14 67-72.
- 66 KENDALL MJ, JACK DB, LAUGHER SJ, LOBO J and SMITH SR  
Lack of a pharmacokinetic interaction between nifedipine and the  $\beta$ -adrenoceptor blockers metoprolol and atenolol  
*Br J Clin Pharmacol* 1984; 18 331-35



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**'Tenormin'**  
**pharmacokinetics**

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# **Contents**

## **'Tenormin'**

### **pharmacokinetics**

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## Consistent bioavailability = predictable clinical response

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**Patients with  
normal renal and  
hepatic  
function**

Bioavailability of 'Tenormin' is reflected in the blood levels of the drug as well as its accumulation in the urine and is a consequence of its minimal metabolism ( $<10\%$ )<sup>1</sup> and low biliary excretion.<sup>2</sup> Approximately 50% of 'Tenormin' is absorbed after oral administration<sup>3-6</sup> and urinary recovery of 'Tenormin' is of the order of 95% (after iv administration)<sup>5</sup> and 50% (oral administration) respectively<sup>5</sup> (see summary in Table 1)

Ingestion of food reduces the mean area-under-the-curve (AUC) values by 20% after acute administration of 'Tenormin'<sup>7</sup> but is unlikely to have any clinical consequences in view of the flat 'Tenormin' dose-response curve (see 'Hypertension' chapter)

Peak plasma levels are reached approximately 2-4 hours after repeated oral dosing (100mg/day) and do not differ

of its negligible liver metabolism.<sup>5</sup> Consequently, consistent blood levels are achieved with a predictable clinical response.

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## Simple kinetic profile gives few clinical problems

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'Tenormin' is only 3% protein bound in the plasma<sup>8</sup> and

The elimination half-life of 'Tenormin' following chronic oral administration to patients with normal renal function is 6-9 hours<sup>3,5,6,10</sup> and is of the same order as

**Table 1. 'Tenormin' – summary of pharmacokinetic data<sup>3,5,13,30</sup>**

	Dose (mg)	$t_{1/2}$ (hours)	Bioavail- ability (%)	Mean $C_{max}$ (ng/ml)	Mean $T_{max}$ (minutes)	Mean $AUC_0-24$ (ng ml <sup>-1</sup> h)	Mean Vol distribution (L/kg)
Oral	100	6-9	50	600	2-4	6000	–
Intravenous	50	6-9	95	–	–	4730	0.7

## Clinically-verified dose recommendations

### Patients with impaired renal function

Values 12-14 Summary statistics obtained after single

Dose recommendations have been calculated in order to avoid excessive blood levels of 'Tenormin'<sup>13</sup> and have been verified in patients with impaired renal function<sup>15</sup> (for further details see Prescribing Information)

## 'Tenormin' – elimination by haemodialysis

'Tenormin' is readily dialysable due to very low

protein binding. The dialysis clearance of 'Tenormin' is approximately 100 ml/min, which is comparable to the

of 50% for each dialysis.<sup>17</sup>

In the dialysis interval, 'Tenormin' is eliminated from the extracellular fluid of treated patients

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## Minimal problems with impaired liver function

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generally unaffected by alterations in liver function<sup>18-20</sup>. Nevertheless, in a small number of patients with chronic liver disease, transient changes in renal function may occur, leading to delayed excretion of 'Tenormin'.<sup>20</sup>

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## Kinetics unaffected by thyroid disease

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## 'Tenormin' and elderly patients

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Renal and hepatic function decrease with age<sup>22,23</sup> and therefore a lipophilic beta-blocker such as metoprolol, which is metabolised, shows marked variations in peak plasma levels in young and elderly subjects.<sup>24</sup> However, 'Tenormin' is virtually unmetabolised and does not accumulate significantly at glomerular filtration rates above 35ml/min.<sup>13</sup>

The kinetics of 'Tenormin' have been compared in young and elderly (66-78 year old) male subjects given single oral (100mg) or intravenous (10mg) doses. There was no significant effect of increasing age on clearance, volume of distribution or bioavailability of 'Tenormin'.<sup>25</sup> The

In contrast, the results of a second study provided a different view. Barber and colleagues calculated



**Table 1. 'Tenormin' – summary of pharmacokinetic data<sup>3,5,13,30</sup>**

	Dose (mg)	t <sub>1/2</sub> (hours)	Bioavailability (%)	Mean C <sub>max</sub> (ng/ml)	Mean T <sub>max</sub> (minutes)	Mean AUC <sub>0-1h</sub> (ng ml <sup>-1</sup> h)	Mean Vol distribution (L/kg)
Oral	100	6.9	50	600	2.4	6000	–
Intravenous	50	6.9	95	–	–	4730	0.7

## Clinically-verified dose recommendations

### Patients with impaired renal function

The peak and 24-hour plasma concentrations of 'Tenormin' increase as creatinine clearance decreases, as demonstrated by an increase in blood half-life and AUC

Dose recommendations have been calculated in order to avoid excessive blood levels of 'Tenormin'<sup>13</sup> and have been verified in patients with impaired renal function<sup>15</sup> (for further details see Prescribing Information).

## 'Tenormin' – elimination by haemodialysis

'Tenormin' is readily dialysable due to very low protein

In the dialytic interval 'Tenormin' is eliminated slowly<sup>17</sup>

ven

Information section)





*is a non-metabolised, cardioselective beta-blocker  
[Tenormin]...<sup>29</sup>*

## Summary: 'Tenormin' pharmacokinetics

- Simple kinetics due to hydrophilic molecule
- Predictable clinical response to a fixed dose
- Low volume of distribution contributes to low CNS penetration with low incidence of side-effects
- Kinetics unaffected by thyroid or liver disease
- Clinically-verified dose recommendations for patients with impaired renal function
- Minimal effect of age on kinetics

# References

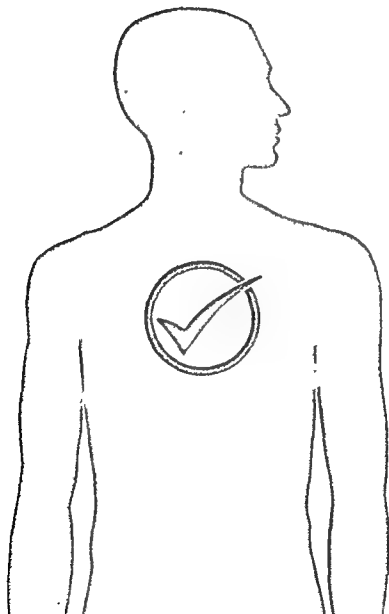
- 1 REEVES PR, McAINSH J, McINTOSH DAD and WINROW MJ  
Metabolism of atenolol in man  
*Xenobiotica* 1978, 8: 313-20
- 2 ESQUIS B, BALANT L, DAYER P *et al*  
Biliary elimination of atenolol: influence on systemic availability?  
*J Pharm Clin* 1982, 1 (1): 43-48
- 3 BROWN HC, CARRUTHERS SG, JOHNSTON GB *et al*  
Clinical pharmacologic observations on atenolol, a beta-adrenoceptor blocker  
*Clin Pharmacol Ther* 1976, 20: 524-34
- 4 FITZGERALD JD, RUFFIN R, SMEDSTAD KG, ROBERTS R and McAINSH J  
Studies on the pharmacokinetics and pharmacodynamics of atenolol in man  
*Eur J Clin Pharmacol* 1978, 13: 81-89
- 5 MASON WD, WINER N, KOCHAK G, COHEN I and BELL R  
Kinetics and absolute bioavailability of atenolol  
*Clin Pharmacol Ther* 1979, 25 (4): 408-15
- 6 WAN SH, KODA RT and MARONDE RF  
Pharmacokinetics, pharmacology of atenolol and effect of renal disease  
*Br J Clin Pharmacol* 1979, 7: 569-74
- 7 MELANDER A, STENBURY P, LIEDHOLM H, SCHIRSTEN B and WATKIN-BOLLE E  
Food induced reduction in bioavailability of atenolol  
*Eur J Clin Pharmacol* 1979, 16: 327-30
- 8 BARBER HE, HAWKSWORTH GM, KITTERINGHAM NR, PATERSEN J, PETRIE JC and SWANN JM  
Protein binding of atenolol and propranolol to human serum albumin and in human plasma.  
*Br J Clin Pharmacol* 1977, 8 (5): 446-47
- 9 NEIL-DWYER G, BARTLETT J, McAINSH J and CRUICKSHANK JM  
 $\beta$ -adrenoceptor blockers and the blood-brain barrier  
*Br J Clin Pharmacol* 1981, 11: 549-53
- 10 KIRCH W, KOHLER H, MUTSCHLER E and SCHAFER M  
Pharmacokinetics of atenolol in relation to renal function  
*Eur J Clin Pharmacol* 1981, 19: 65-71
- 11 AMERY A, DE PLAEN JF, McAINSH J and  
McAINSH J  
*Clin Pharmacol Ther* 1980, 28 (3): 302-309
- 12 McAINSH J, HOLMES BF, SMITH S, HOOD D and WARREN D  
Atenolol kinetics in renal failure  
*Clin Pharmacol Ther* 1980, 28 (3): 302-309
- 13 SASSARD J, POZET N, McAINSH J, LEGHEAND J and ZECH P  
Pharmacokinetics of atenolol in patients with renal impairment  
*Eur J Clin Pharmacol* 1977, 12: 175-80
- 14 WARREN DJ, WALLER DG and McAINSH J  
Beta-blockers and renal function  
*Drugs* 1983, 25 (Suppl 2): 108-12
- 15 SEILER KU, ALBRECHT HU, NIEDERMAYER W and WASSERMAN O  
Effect of liver function on beta-blocker kinetics  
*Drugs* 1983, 25 (Suppl 2): 113-20
- 16 LEBREC D, FLOUVAT B, DECOURT S and DUPONT C  
Atenolol and liver function  
*Drugs* 1983, 25 (Suppl 2): 147
- 17 KIRCH W, SCHAFER-KORTING M, MUTSCHLER E, OHNHAUS EE and BRAUN W  
Clinical experience with atenolol in patients with chronic liver disease  
*J Clin Pharmacol* 1983, 23: 171-77
- 18 HALLENGREN B, NILSSON OR, KARLBERG BE *et al*  
Influence of hyperthyroidism on the kinetics of methimazole, propranolol, metoprolol and atenolol  
*Eur J Clin Pharmacol* 1982, 21 (5): 379-84

- 22 DAVIES DF and SHOCK NW  
Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males  
*J Clin Invest* 1950, 29: 496
- 23 THOMPSON EN and WILLIAMS R  
Effect of age upon liver function with particular reference to bromsulphthalein excretion  
*Gut* 1965, 6: 266
- 24 JOHNSSEN G and REGARDH CG  
Clinical pharmacokinetics of beta-adrenoceptor blockers  
*Drugs* 1976, 11: 111-21
- 25 RUBIN PC, SCOTT PJW, McLEAN K, PEARSON A, ROSS H and REID JL  
Atenolol disposition in young and elderly subjects  
*Br J Clin Pharmacol* 1982, 13: 235-37
- 26 BARBER HE, HAWKSWORTH GM, PETRIE JC, RIGBY JW, ROBB OJ and SCOTT AK  
Pharmacokinetics of atenolol and propranolol in young and elderly subjects  
*Br J Clin Pharmacol* 1981, 11 (1) 118-19
- 27 O'MALLEY K and O'BRIEN ET  
Antihypertensive treatment with beta-blockers in patients aged over 65  
*Br Med J* 1981, 285 (6354) 1571
- 28 CRUICKSHANK JM  
Beta-blockers, bradycardia and adverse effects  
*Acta Ther* 1981, 7: 309-21
- 29 ZACHARIAS FJ and CRUICKSHANK JM  
Treating the elderly hypertensive  
*Acta Ther* 1979, 5: 179-92

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## **Tolerability of 'Tenormin'**

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## Tolerability of

### 'Tenormin'

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extremely low

In general, the reporting of the incidence of side-effects varies enormously with the evaluation technique employed. It is recognised that the incidence of "events" (synonymous with adverse reactions or side-effects) is

inability to establish a causal link between drug and "events".

One of the most reliable methods is that based on a double-blind, placebo-controlled trial where the placebo effects can be subtracted from the effects of the active drug. Several of these studies as well as large-scale patient surveys have been used to assess the tolerability profile of 'Tenormin'. Some of the adverse reactions have been classified into those which can be predicted from the pharmacological properties of the molecule and those which are idiosyncratic.

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### Most studies show only minor side-effects with 'Tenormin'

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#### Double-blind trials

In 11 separate double-blind, randomised trials, side-effects were assessed in 482 patients with mild to moderate hypertension. Their ages ranged from 18-65 years and they received 'Tenormin' (100-300mg daily) or placebo for at least one month before answering questions from a symptom check list.<sup>2</sup>

Cold extremities and fatigue were seen more often with 'Tenormin' and their incidence accounted almost exclusively for the higher total incidence of side-effects in the 'Tenormin'-treated group (Table 1)



**Table 1: Adverse effects of 'Tenormin' and placebo (n=482).**

Side-effects	Placebo		'Tenormin'	
	n	%	n	%
Cold extremities	47	9.8	75	15.6
Fatigue	82	17.0	107	22.2
Bronchospasm	27	5.6	30	6.2
Indigestion	16	3.3	16	3.3
Diarrhoea	2	0.4	7	1.5
Constipation	24	5.0	13	2.7
Vivid dreams	17	3.5	14	2.9
Insomnia	12	2.5	9	1.9
Dizziness	31	6.4	37	7.7
Depression	30	6.2	26	5.4
Impotence	12	2.5	13	2.7
Paraesthesia	10	2.1	13	2.7
Skin rash	4	0.8	3	0.6
Ataxia	1	0.2	3	0.6
Total	315		366	

Other physicians have similarly noted that the "true"

**95% of patients report feelings of well-being**

... .. of the group.<sup>6</sup>

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**Table 2. Twenty most frequently reported side-effects based on 39,745 patients.**

Adverse effect	Number reported	Percent
Headache	628	1.6
Dizziness	628	1.6
Tiredness	497	1.3
Nausea	461	1.2
Fatigue	439	1.1
Weakness	375	0.9
Lightheadedness	268	0.7
Bradycardia	232	0.6
Oedema	216	0.5
Diarrhoea	203	0.5
Depression	184	0.5
Impotence	149	0.4
Dyspnoea	144	0.4
Nervousness	141	0.4
Chest pain	126	0.3
Lethargy	117	0.3
Malaise	115	0.3
Dry mouth	111	0.3
Drowsiness	108	0.3
Increased blood pressure	105	0.3

## Long-term tolerability

because of side-effects, the most common reason being

**Table 1: Adverse effects of 'Tenormin' and placebo (n=482).**

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Insomnia	12	2.5	9	1.9
Dizziness	31	6.4	37	7.7
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Impotence	12	2.5	13	2.7
Paraesthesia	10	2.1	13	2.7
Skin rash	4	0.8	3	0.6
Ataxia	1	0.2	3	0.6
Total	315		366	

Other physicians have similarly noted that the "true" side-effects of 'Tenormin', reported by patients, were muscle fatigue and cold extremities.<sup>3</sup> The overall number of side-effects to 'Tenormin' treatment was equally low in other double-blind studies.<sup>4,5</sup>

## 95% of patients report feelings of well-being

A large postmarketing surveillance study was conducted in a predominantly middle-aged to elderly population of 39,745 hypertensive patients, 34,120 of whom completed 28 days' treatment with 'Tenormin'. These patients were treated for one month with 50mg 'Tenormin' daily, which produced satisfactory blood pressure control in 71-80% of the group.<sup>6</sup>

A high percentage of well-being was reported by 95% of

physicians. The twenty most reported side-

reason for stopping or changing 'Tenormin' treatment. Further evidence is provided by Simpson who had to withdraw only one patient out of a group of 543 because of symptomatic bradycardia.<sup>18</sup>

the frequency of dizziness, fatigue and cold extremities was similar in all age groups, indicating that the elderly were not likely to experience any extra problems. Additionally, in a subgroup of 482 patients who received 'Tenormin' for at least one month, the reported frequency of dizziness was similar to placebo (Table 1).<sup>2</sup>

### Minimal incidence of heart failure

Heart failure has rarely been reported with 'Tenormin'.<sup>9,19</sup> Furthermore, in patients with myocardial infarction, a reduction in the incidence of heart failure, from 24% in controls to 19%, was recorded after acute intervention with 'Tenormin'.<sup>17</sup> A second study involving myocardial infarction patients also recorded a lower incidence of heart failure after 'Tenormin' compared with placebo or propranolol treatment.<sup>20</sup>

This beneficial action of 'Tenormin' may be due to a reduction in infarct size and consequently preservation of a viable myocardium

### No requirement for additional inotropic agents

infarction.<sup>21</sup>

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## The advantages of cardioselectivity

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The advantages of cardioselective 'Tenormin' for a wide variety of patients and, in particular, for the asthmatic and diabetic patient, have already been described in the 'Cardioselectivity' chapter.

Whilst reports of cold extremities are common to all

survey of patients who completed self-assessment questionnaires showed that cold digits were perceived

### Low risk of cold extremities

indigestion ( $n=3$ ). "Prohibitive" side-effects such as bronchospasm occurred much less frequently with

and propranolol-treated patients (14.4%) as did the minor "tolerable" side-effects ■

A further large open study has confirmed the good tolerability of 'Tenormin'.<sup>10</sup>

## Comparison with other antihypertensive drugs

A number of studies have attempted to define the overall

in routine use.

The total incidence of side-effects was generally similar

With methyldopa, "... most patients do not realize that they have been suffering from tiredness or drowsiness until they change to another drug regime"<sup>12</sup>

---

## Incidence of side-effects is not related to pharmacological profile

---

## Influence of heart rate

Slowing of the heart rate is a consequence of the  
use of beta-blockers including  
cal  
17

the incidence of side-effects

## **The benefits of hydrophilicity by substituting 'Tenormin' in place of lipophilic beta-blockers**

The hydrophilic nature of 'Tenormin' is reflected in a very low frequency of CNS side-effects. The other major benefits of hydrophilicity are discussed in more depth in the 'Hydrophilicity' chapter.

In various trials, including double-blind and randomised studies, the use of lipophilic beta-blockers has been

abolished.

drug<sup>37,39-43</sup> Reports of sleep disturbances, insomnia and restless nights were all significantly lower with 'Tenormin' than pindolol or metoprolol<sup>37,39,41</sup>

Patients who received 'Tenormin' as a substitute medication reported a significant preference ( $p < 0.05$ ) for 'Tenormin' over metoprolol and propranolol<sup>40</sup> and had fewer CNS problems such as nightmares, hallucinations<sup>40</sup> and visual perceptual disorders.<sup>42</sup> One investigator concluded, "CNS side effects on  $\beta$ -blockers . . . can be very unpleasant for the individual

'Tenormin' in view of its hydrophilic properties<sup>43</sup> The patient response to this change in medication was monitored over 1-4 years and is summarised in Table 3 The investigators concluded, "[Tenormin] seems to give much less problems [with] the CNS and this impression has been maintained during more than 1000 patient-years"<sup>43</sup>

least often with 'Tenormin' compared with other beta-blockers including non-selective agents, the incidence being similar to placebo.<sup>23</sup>

## Low risk of fatigue

There is no evidence that 'Tenormin' causes fatigue. In fact, 'Tenormin' has been shown to have a beneficial effect on physical performance compared with non-selective beta-blockers. Overall, beta-blockers did not inhibit the response to physical training<sup>24</sup> however, non-selective agents such as propranolol and pindolol caused more impairment of physical performance (maximum exercise load and exercise duration)<sup>25-28</sup> than 'Tenormin' and this was particularly noticeable in subjects with a high percentage of slow-twitch muscle fibres.<sup>25</sup> 'Tenormin' also

causes less fatigue than non-selective beta-blockers.

In one other study, fatigue developed early in treatment with 'Tenormin' but resolved spontaneously after 2-3 weeks or with a reduction in dosage.<sup>32</sup>

## Lipoproteins

'Tenormin' has been shown to have a beneficial effect on

lipoprotein metabolism.<sup>33</sup>

## Glucose tolerance

'Tenormin' has been shown to have a beneficial effect on

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## Non-pharmacological (idiosyncratic) side-effects of 'Tenormin' are rare

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placebo or not at all.<sup>2,18</sup> However, isolated case reports of skin rashes due to beta-blockers including 'Tenormin' have been published.<sup>49-51</sup>

Gastrointestinal symptoms such as diarrhoea, constipation and indigestion all occurred at placebo level as did impotence and depression (Table 1).<sup>2</sup>

The oculomucocutaneous syndrome, described for practolol, has not been reported with 'Tenormin' and in 14 patients who developed the syndrome on practolol, all improved on switching to 'Tenormin'.<sup>8</sup>

### Laboratory values

SGOT, SGPT, bilirubin, alkaline phosphatase, serum urate and creatinine or urinary glucose and protein.<sup>4</sup>

---

## The elderly do not experience more side-effects with 'Tenormin' than younger patients

---

### Effect of age on side-effects

In the large patient survey described earlier in this chapter, the elderly experienced no more side-effects than younger patients<sup>2</sup> and this was confirmed by a further study in the elderly.<sup>52</sup>

A controlled trial is currently underway to test the

group, completed self-administered questionnaires



**Table 3. Patient response to medication changeover (lipophilic beta-blocker to 'Tenormin').**

Symptoms	Number of reports	Symptom disappeared or clearly improved (%)
Nightmares, insomnia and/or hallucinations	55	91
Fatigue and/or depression	42	60
Gastrointestinal trouble	26	85
Bronchospasm	16	94
Impotence	8	33
Cold hands	6	50

Other subjective and objective effects of various beta-

15mg/day).

'Tenormin' was indistinguishable from placebo and produced significantly fewer reports of dreams than

waking than pindolol and propranolol (p < 0.05). A disturbance of the sleep EEG was noted with pindolol.

Further supportive evidence has been published in a study of the substitution of 'Tenormin' in place of other beta-blockers. In this study, 100 patients who had been on various beta-blockers for at least 6 months were substituted with 'Tenormin' for their previous beta-blocker medication.

However, in order to minimise risk it is recommended that, in patients with ischaemic heart disease, withdrawal of 'Tenormin' should be gradual (see Prescribing Information section)

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## Few problems with 'Tenormin' even in overdose

---

### Tolerability in overdose

Beta-blockers are agents with a high benefit-to-risk ratio and very large doses are usually well tolerated. The clinical outcome of beta-blocker overdose can be

unless other drugs or alcohol had also been consumed.<sup>57</sup>

One case has been reported of a patient who ingested

uncomplicated.<sup>58</sup>

One of the highest known overdoses with 'Tenormin' 100mg

combination of digoxin, verapamil and a morphine derivative.<sup>59</sup> He was admitted 1½ hours later and

incomplete right-sided block and grade I AV block. There were no signs of heart failure.

After treatment, he made a full recovery and no 'Tenormin' was detectable in his serum four days after the overdose.<sup>59</sup>

### Summary:

#### Tolerability of 'Tenormin'

- Tolerability profile confirmed in large patient studies
- Less than 3% withdrawal rate due to drug intolerance
- Similar incidence of side-effects to placebo except for the well-documented beta-blocker side-effects of fatigue and cold extremities
- Hydrophilic and cardioselective properties confer important benefits in the form of a low incidence of side-effects
- No changes in hepatic or renal function
- No changes in laboratory values
- Little evidence of withdrawal phenomena although caution is recommended
- Well-tolerated even in overdose

Preliminary analysis of questionnaires showed that the treated group had a similar level of complaints to the untreated and control groups (Table 4).<sup>53</sup>

**Table 4. Side-effects in elderly hypertensive patients.**

Incidence (%) in each group			
Side-effect	Normotensive patients*	Hypertensive controls treated	
Headache	17	19	19
Tiredness	63	51	58
Breathlessness	55	37	51
Vertigo	38	23	26
Depression	13	17	14
Indigestion	35	29	29
"Worries"	44	30	30
Generally unwell	32	24	35

\*1 in 5 sample

## Little evidence for involvement of 'Tenormin' in beta-blocker withdrawal syndrome

Controversy surrounds the exact nature of the "beta-blocker withdrawal syndrome" and whether it is a real phenomenon. The conflicting evidence has included anecdotal reports as well as controlled studies and the "syndrome" generally occurred in patients receiving propranolol.<sup>54</sup>

The effects of abrupt withdrawal of 'Tenormin' treatment have recently been examined in a group of 20 patients

these subjects and it was concluded, "... the clinical consequences of abrupt ['Tenormin'] withdrawal are usually minor and predictable corresponding with a gradual disappearance of beta-blockade over several days."<sup>55</sup>

- 25 KAISER P, ROSSNER S and KARLSON J  
Effects of  $\beta$  adrenergic blockade on endurance  
and short time performance in respect to  
individual muscle fiber composition  
*Int J Sports Med* 1981, 2 37-42.
- 26 KAISER P  
Physical performance and muscle metabolism  
during  $\beta$ -adrenergic blockade in man. Comparison  
between  $\beta_1$ -selective and non-selective  $\beta$  blockade  
with regard to work capacity  
*Acta Physiol Scand* 1984, 122 (Suppl 536)  
29-30
- 27 KAISER P  
Physical performance and muscle metabolism  
*Acta Physiol Scand* 1984, 122 (Suppl 536)  
29-30
- 28 QUYYUMI AA, WRIGHT C, MOCKUS L and  
FOX KM  
Effect of partial agonist activity in  $\beta$  blockers in  
severe angina pectoris. A double-blind  
comparison of pindolol and atenolol  
*Br Med J* 1984, 289 951-53
- 29 KIRK CA and COVE-SMITH R  
A comparison between atenolol and metoprolol in  
respect of central nervous system side-effects  
*Postgrad Med J* 1983, 59 (Suppl 3), 161-63
- 30 GORDON NF, KRUGER PE, VAN RENSBERG  
JP, VAN DER LINDE A, KIELBLOCK A and  
CHILERS JF  
Effects of  $\beta$ -adrenoceptor blockade on  
thermoregulation during prolonged exercise  
*J Appl Physiol* 1985, 58 (3) 899-906
- 31 KIRK CA and COVE-SMITH R  
A comparison between atenolol and metoprolol in  
respect of central nervous system side-effects  
*Postgrad Med J* 1983, 59 (Suppl 3), 161-63
- 32 FLEMINGER R  
Visual perceptual disorders and other central  
nervous system side-effects. A comparison  
between propranolol and atenolol  
Sixth Scientific Meeting of the International  
Society of Hypertension, Gothenburg, June 11-  
13th, 1979 (Abstract)
- 33 MATTIASSEN I and HENNINGSON NC  
Side-effects during treatment with lipid-soluble  
beta-adrenergic-blocking substances  
Eighth World Congress of Cardiology, Tokyo,  
Sept. 17-23rd, 1978, Abstract 1097 365
- 34 BETTS TA and ALFORD C  
Beta-blocking drugs and sleep. A controlled trial  
*Drugs* 1983, 25 (Suppl 2) 268-72
- 35 FRASER HS and CARR AC  
Propranolol psychosis  
*Br J Psychiatry* 1976, 129 508-509
- 36 McNEIL GN, SHAW PK and DOCK DS  
Substitution of atenolol for propranolol in a case  
of propranolol-related depression  
*Am J Psychiatry* 1982, 139 (9) 1187-88
- 35 DAY JL, SIMPSON N, METCALFE J and PAGE  
RL  
Metabolic consequences of atenolol and  
propranolol in treatment of essential  
hypertension  
*Br Med J* 1979, 1 (6156) 77-80
- 36 DAY JL, METCALFE J and SIMPSON N  
Adrenergic mechanisms in the control of plasma  
lipids  
*Br Med J* 1982, 284 1145-48
- 37 ROSSNER S and WEINER L  
A comparison of the effects of atenolol and  
metoprolol on serum lipoproteins  
*Drugs* 1983, 25 (Suppl 2) 322-25
- 38 IBRAHIM MM and MOSSALLAM R  
Clinical evaluation of atenolol in hypertensive  
patients  
*Circulation* 1981, 64 368-74
- 39 GREMINGER P, VETTER H, BOERLIN H *et al*  
A comparative study between 100mg atenolol and  
20mg pindolol slow-release in essential  
hypertension  
*Drugs* 1983, 25 (Suppl 2) 37-41
- 40 WESTERLUND A  
A comparison of the central nervous system  
side-effects caused by lipophilic and hydrophilic  
beta blockers  
*Drugs* 1983, 25 (Suppl 2) 280-81
- 41 KIRK CA and COVE-SMITH R  
A comparison between atenolol and metoprolol in  
respect of central nervous system side-effects  
*Postgrad Med J* 1983, 59 (Suppl 3), 161-63
- 42 FLEMINGER R  
Visual perceptual disorders and other central  
nervous system side-effects. A comparison  
between propranolol and atenolol  
Sixth Scientific Meeting of the International  
Society of Hypertension, Gothenburg, June 11-  
13th, 1979 (Abstract)
- 43 MATTIASSEN I and HENNINGSON NC  
Side-effects during treatment with lipid-soluble  
beta-adrenergic-blocking substances  
Eighth World Congress of Cardiology, Tokyo,  
Sept. 17-23rd, 1978, Abstract 1097 365
- 44 BETTS TA and ALFORD C  
Beta-blocking drugs and sleep. A controlled trial  
*Drugs* 1983, 25 (Suppl 2) 268-72
- 45 FRASER HS and CARR AC  
Propranolol psychosis  
*Br J Psychiatry* 1976, 129 508-509
- 46 McNEIL GN, SHAW PK and DOCK DS  
Substitution of atenolol for propranolol in a case  
of propranolol-related depression  
*Am J Psychiatry* 1982, 139 (9) 1187-88

# References

- 3 MARSHALL AJ, ROBERTS CJ and BARRITT DW  
Raynaud's phenomenon as side-effect of beta blockers in hypertension  
*Br Med J* 1976, 1 1498
- 5 DOUGLAS-JONES AP and CRUICKSHANK JM  
Once-daily dosing with atenolol in patients with mild or moderate hypertension  
*Br Med J* 1976, 1 990-91
- 7  
*Curr Ther Res* 1983, 33 (1) 165-71
- 8 ZACHARIAS FJ, CUTHBERTSON PJR, PRESTI J *et al*  
Atenolol in hypertension: a study of long-term therapy  
*Postgrad Med J* 1977, 53 (Suppl 3) 102-10
- 9 ZACHARIAS FJ  
Patient acceptability of propranolol and the occurrence of side-effects  
*Postgrad Med J* 1976, 52 (Suppl 4) 87-89
- 10 INGRAM DF  
Interim report on a compliance study and review of side-effects  
*Proc R Soc Med* 1977, 70 (Suppl 5) 54-55
- 11 HUSSERL FE and MESSERLI FH  
Adverse effects of antihypertensive drugs  
*Drugs* 1981, 22 188-210
- 12 PAYKEL ES, FLEMINGER II and WATSON JP  
Psychiatric side-effects of antihypertensive drugs other than reserpine  
*J Clin Psychopharmacol* 1982, 2 (1) 14-39
- 13 REICHGOTT MJ  
Problems of sexual function in patients with hypertension  
*Cardiovasc Med* 1979, 4 (2) 149-56
- 14 MRC WORKING PARTY ON MILD TO MODERATE HYPERTENSION  
Adverse reactions to bendroflumazide and propranolol for the treatment of mild hypertension  
*Lancet* 1981, 2 539-43
- 15  
suspected acute myocardial infarction  
*Drugs* 1983, 25 (Suppl 2) 303-307
- 18 SIMPSON WT  
Nature and incidence of unwanted effects with atenolol  
*Postgrad Med J* 1977, 53 (Suppl 3) 162-67.
- 19 CASTLEDEN CM, DATHAN JRE and GEORGE CF  
A comparison of once- and twice-daily atenolol in hypertension  
*Postgrad Med J* 1977, 53 679-82.
- 20 WILCOX RG, ROLAND JM, HANKS DC, HAMPTON JR and MITCHELL JRA  
Randomised trial comparing propranolol with atenolol in immediate treatment of suspected myocardial infarction  
*Br Med J* 1980, 280 (6218) 885-88
- 21 MIAMI TRIAL RESEARCH GROUP  
Metoprolol in acute myocardial infarction (MIAMI) A randomised placebo-controlled international trial  
*Eur Heart J* 1985, 6 199-226
- 22 WARREN DJ, MCSORLEY P and NAIK RB  
Effects of beta-adrenergic blocking drugs on peripheral blood flow  
Eighth World Congress of Cardiology, Tokyo, 1978, (Abstract)
- 23 LEWIS RV, JACKSON P and RAMSAY LE  
A comparison of  $\beta$ -adrenoceptor blocker side-effects using visual analogue scales  
*Br J Clin Pharmacol* 1984, 17 (5) 633-34p
- 24  
*Br Heart J* 1982, 48 33-38

- 25 KAISER P, ROSSNER S and KARLSON J  
Effects of  $\beta$ -adrenergic blockade on endurance and short time performance in respect to individual muscle fiber composition  
*Int J Sports Med* 1981; 2: 37-42.
- 26 KAISER P  
Physical performance and muscle metabolism during  $\beta$ -adrenergic blockade in man. Comparison between  $\beta_1$ -selective and non-selective  $\beta$  blockade with regard to work capacity  
*Acta Physiol Scand* 1984, 122 (Suppl. 536) 29-30
- 27 KAISER P  
Physical performance and muscle metabolism during  $\beta$ -adrenergic blockade in man. Effect of  $\beta_1$ -selective blockade on muscle metabolism  
*Acta Physiol Scand* 1984, 122 (Suppl. 536) 31-32
- 28 QUYYUMI AA, WRIGHT C, MOCKUS L and FOX KM  
Effect of partial agonist activity in  $\beta$  blockers in severe angina pectoris. A double-blind comparison of pindolol and atenolol.  
*Br Med J* 1984, 289: 951-53
- 29 GORDON NF, KRUGER PE, VAN RENSBURG JP, VAN DER LINDE A, KIELBLOCK A and CILLIERS JF  
Effects of  $\beta$ -adrenoceptor blockade on thermoregulation during prolonged exercise  
*J Appl Physiol* 1985, 58 (3): 899-906  
*Lancet* 1978, 2: 424-25
- 30 CHIN R  
Effects of  $\beta$ -adrenoceptor blockade on thermoregulation during prolonged exercise  
*J Appl Physiol* 1985, 58 (3): 899-906
- 31 KROGER  
Effects of  $\beta$ -adrenoceptor blockade on thermoregulation during prolonged exercise  
*J Appl Physiol* 1985, 58 (3): 899-906
- 32 DAY JL, SIMPSON N, METCALFE J and PAGE RL  
Metabolic consequences of atenolol and propranolol in treatment of essential hypertension.  
*Br Med J* 1979, 1 (6156) 77-80
- 33 DAY JL, METCALFE J and SIMPSON N  
Adrenergic mechanisms in the control of plasma lipids  
*Br Med J* 1982, 284: 1145-48
- 34 ROSSNER S and WEINER L  
A comparison of the effects of atenolol and metoprolol on serum lipoproteins.  
*Drugs* 1983, 25 (Suppl. 2) 322-25
- 35 IBRAHIM MM and MOSSALLAM R  
Clinical evaluation of atenolol in hypertensive patients  
*Circulation* 1981, 64: 368-74
- 36 GREMMINGER P, VETTER H, BOERLIN HJ *et al*  
A comparative study between 100mg atenolol and 20mg pindolol slow release in essential hypertension  
*Drugs* 1983, 25 (Suppl. 2) 37-41
- 37 WESTERLUND A  
A comparison of the central nervous system side-effects caused by lipophilic and hydrophilic beta blockers.  
*Drugs* 1983, 25 (Suppl. 2) 280-81
- 38 KIRK CA and COVE-SMITH R  
A comparison between atenolol and metoprolol in respect of central nervous system side-effects  
*Postgrad Med J* 1983, 59 (Suppl. 3), 161-63
- 39 FLEMINGER R  
Visual perceptual disorders and other central nervous system side-effects. A comparison between propranolol and atenolol  
Sixth Scientific Meeting of the International Society of Hypertension, Gothenburg, June 11-13th, 1979 (Abstract)
- 40 BETTS TA and ALFORD C  
Beta-blocking drugs and sleep. A controlled trial  
*Drugs* 1983, 25 (Suppl. 2) 268-72.
- 41 FRASER HS and CARRAC  
Propranolol psychosis  
*Br J Psychiatry* 1976, 129: 508-509
- 42 McNEIL GN, SHAW PK and DOCK DS  
Substitution of atenolol for propranolol in a case of propranolol-related depression.  
*Am J Psychiatry* 1982, 139 (9) 1187-88

# References

- 1 RICHARDS DJ and RONDEL RK  
Eds Adverse drug reactions Their prediction,  
detection and assessment (AMAPI Symposium)  
London, Churchill Livingstone, 1972
- 2 CRUICKSHANK JM  
Beta-blockers, bradycardia and adverse effects  
*Acta Ther* 1981, 7 309-21
- 3 MARSHALL AJ, ROBERTS CJ and  
BARRITT DW  
Raynaud's phenomenon as side-effect of beta  
blockers in hypertension  
*Br Med J* 1976, 1 1498
- 4 HANSSON L, ABERG H, KARLBERG BE and  
WESTERLUND A  
Controlled study of atenolol in treatment of  
hypertension  
*Br Med J* 1975, 1 367-70
- 5 DOUGLAS-JONES AP and  
CRUICKSHANK JM  
Once-daily dosing with atenolol in patients with  
mild or moderate hypertension  
*Br Med J* 1976, 1 990-91
- 6 HERMAN RL, LAM DIN E and FISCHETTI JL  
Postmarketing evaluation of atenolol ('Tenormin')  
a new cardioselective beta-blocker  
*Curr Ther Res* 1983, 33 (1) 165-71
- 7 CONTI LMZ, BALDEZ D and LEITE FBT  
Evaluation of routine clinical use of atenolol in the  
control of arterial hypertension  
*Folha Med* 1983, 87 (2) 105-109
- 8 ZACHARIAS FJ, CUTHBERTSON PJR,  
PREST J *et al*  
Atenolol in hypertension: a study of long-term  
therapy  
*Postgrad Med J* 1977, 53 (Suppl 3) 102-10
- 9 ZACHARIAS FJ  
Patient acceptability of propranolol and the  
occurrence of side-effects  
*Postgrad Med J* 1976, 52 (Suppl 4) 87-89
- 10 INGRAM DF  
Interim report on a compliance study and review  
of side-effects  
*Proc R Soc Med* 1977, 70 (Suppl 5) 54-55
- 11 HUSSERL FE and MESSERLI FH  
Adverse effects of antihypertensive drugs  
*Drugs* 1981, 22 188-210
- 12 PAYKEL ES, FLEMINGER R and WATSON JP  
Psychiatric side-effects of antihypertensive drugs  
other than reserpine  
*J Clin Psychopharmacol* 1982, 2 (1) 14-39
- 13 REICHGOTT MJ  
Problems of sexual function in patients with  
hypertension  
*Cardiovasc Med* 1979, 4 (2) 149-56
- 14 BULPITT CJ, HOFFBRAND BI and  
DOLLERY CT  
Contribution of drug treatment to symptoms of  
hypertensive patients In Gross F, ed Mild  
hypertension. Natural history and management.  
Proceedings of the joint WHO/ISH Meeting,  
Susono, Japan, 1979 291-302
- 15 MRC WORKING PARTY ON MILD TO  
MODERATE HYPERTENSION  
Adverse reactions to bendroflumazide and  
propranolol for the treatment of mild  
hypertension  
*Lancet* 1981, 2 539-43
- 16 SLAG MF, MORLEY JE, ELSON MK *et al*  
Impotence in medical clinic outpatients  
*JAMA* 1983, 249 (15) 1756-60
- 17 YUSUFS, ROSSI P, RAMSDALE D *et al*  
Reduction in infarct size, arrhythmias, chest pain  
and morbidity by early intravenous  $\beta$ -blockade in  
suspected acute myocardial infarction  
*Drugs* 1983, 25 (Suppl 2) 503-507.
- 18 SIMPSON WT  
Nature and incidence of unwanted effects with  
atenolol  
*Postgrad Med J* 1977, 53 (Suppl 3) 162-67.
- 19 CASTLEDEN CM, DATHAN JRE and  
GEORGE CF  
A comparison of once- and twice-daily atenolol in  
hypertension  
*Postgrad Med J* 1977, 53 679-82
- 20 WILCOX RG, ROLAND JM, BANKS DC,  
HAMPTON JR and MITCHELL JRA  
Randomised trial comparing propranolol with  
atenolol in immediate treatment of suspected  
myocardial infarction  
*Br Med J* 1980, 280 (6218) 885-88
- 21 MIAMI TRIAL RESEARCH GROUP  
Metoprolol in acute myocardial infarction  
(MIAMI) A randomised placebo-controlled  
international trial  
*Eur Heart J* 1983, 6 199-226
- 22 WARREN DJ, McSORLEY P and NAIK RB  
Effects of beta-adrenergic blocking drugs on  
peripheral blood flow  
Eighth World Congress of Cardiology, Tokyo,  
1978, (Abstract)
- 23 LEWIS RV  
Ac  
effects  
*Br J* 1983, 633-34p
- 24 VANHEES L, FAGARD R and AMERY A  
Influence of beta-adrenergic blockade on effects of  
physical training in patients with ischaemic heart  
disease  
*Br Heart J* 1982, 48 33-38







daily or 100 mg once every two days. For patients, with a creatinine clearance of  $< 15 \text{ ml/min/1.73 m}^2$  (equivalent to serum creatinine of  $> 600 \text{ micromol/litre}$ ) the oral dose should be 50 mg on alternate days or 100 mg once every four days.

Patients on haemodialysis should be given 50 mg orally after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

### **Pregnancy**

'Tenormin' has been used effectively under close supervision for the treatment of pregnancy-associated hypertension. There was no evidence of any foetal abnormalities although 'Tenormin' was generally given after 20 weeks gestation.

'Tenormin' crosses the placental barrier and appears in cord blood. There is an approximate three-fold accumulation of 'Tenormin' in the breast milk. However, there were no apparent detrimental effects in the baby at birth or during breast feeding.

The possibility of foetal injury cannot be excluded and the use of the drug in women who are, or may become pregnant or who are nursing the newborn infant, requires that anticipated benefits be weighed against possible risks.

### **SIDE EFFECTS**

In clinical studies, the side effects reported are usually attributable to its pharmacological actions and include coldness of the extremities, muscular fatigue and, in isolated cases, bradycardia. Sleep disturbances of the type noted with other beta-adrenoceptor blocking drugs have rarely been reported.

There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and in most cases the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable.

### **OVER DOSAGE**

From first principles, excessive bradycardia may be

injection. Care must be taken to ensure that the blood pressure does not fall too low if the dose of the beta-receptor agonist has to be increased.

Glucagon has also been reported to be useful as a cardiac stimulant in a dose of 10 mg intravenously.

### **PRESENTATION**

'Tenormin' tablets each containing atenolol 100 mg and 50 mg.

\*Trademarks

# TENORMIN® – Prescribing Information

## USES

### *a) Control of hypertension*

*'Tenormin' is effective for at least 24 hours after a single oral dose. This facilitates compliance by its*

must be maintained and signs of failure controlled with digitalis and diuretics.

*One of the pharmacological actions of 'Tenormin' is to reduce heart rate. In the rare instances when symptoms may be attributable to the slow heart rate, the dose may be reduced*

*'Tenormin' modifies the tachycardia of hypoglycaemia*

*'Tenormin' may be used with caution in patients with chronic obstructive airways disease. However, occasionally some increase in airways resistance may occur in asthmatic patients. In contrast to non-selective betablockers, this bronchospasm may usually be reversed by commonly used dosage of bronchodilators such as salbutamol or isoprenaline.*

*In patients suffering from ischaemic heart disease, as with other beta-blocking agents, treatment should not be discontinued abruptly.*

*Care should be taken in prescribing a beta-adrenoceptor blocking drug with Class I antidysrhythmic agents such as disopyramide.*

*Beta-adrenoceptor blocking drugs should be used with caution in combination with verapamil in*

## DOSAGE AND ADMINISTRATION

### Adults

#### Hypertension:

Most patients respond to 50-100 mg daily given orally as a single dose. The effect will be fully established after one to two weeks. A further reduction in blood pressure may be achieved by combining 'Tenormin' with other antihypertensive agents. For example, co-administration of 'Tenormin' with a diuretic provides a highly effective and convenient antihypertensive therapy

#### Angina:

Most patients with angina pectoris will respond to 100 mg daily given orally as a single or divided dose. It is unlikely that additional benefit will be gained by increasing the dose

#### Children

There is no paediatric experience with 'Tenormin' and for this reason it is not recommended for use in children

## CONTRAINDICATIONS

'Tenormin' is contraindicated in patients with second degree or third degree heart block. 'Tenormin' should not be used in patients with cardiogenic shock.

## PRECAUTIONS

Special care should be taken with patients whose cardiac reserve is poor. Myocardial contractility

Caution should be exercised when transferring

### Anaesthesia

### Renal failure

ml/min/1.73 m<sup>2</sup> (equivalent to serum creatinine of 300-600 micromol/litre) the oral dose should be 50 mg

- smoking and  
 'Tenormin' in 77, 79, 144  
*cf* nifedipine 77-79, 145  
*cf* propranolol 76, 77, 145  
 S-T segment changes 79, 145
- Angina, unstable  
 beta-blockers in 82, 83, 87  
 'Tenormin' in  
   attack rate 82  
   *cf* calcium antagonists 82, 84, 85  
   + calcium antagonists 84, 85  
   efficacy 82, 83, 85  
   exercise capacity 82  
   heart rate 83  
   *cf* isosorbide mononitrate (ISMN) 82  
   *cf* pindolol 83
- Angiotensin converting  
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Figure 1. The effect of the concentration of the *Agrobacterium* suspension on the transformation efficiency of *Agrobacterium* strains.

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